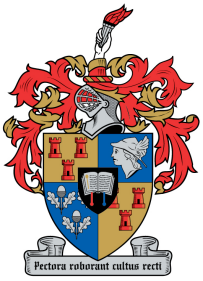
Mathematical modelling to project the impact of interventions targeted to previously treated individuals on the trajectory of the tuberculosis epidemic in high tuberculosis prevalence settings

Florian Michael Marx



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Dissertation presented for the degree of Doctor of Philosophy in the Faculty of Medicine and Health Sciences at Stellenbosch University

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Co-supervisor: Professor Theodore Cohen

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DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third-party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: 26 October 2017

This dissertation includes 2 original papers and 1 letter to the editor published in peer-reviewed journals, and 2 unpublished manuscripts. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and, for each of the cases where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contribution of co-authors.

DECLARATION OF THE CANDIDATE'S CONTRIBUTION TO THE DISSERTATION

I herewith declare the nature and scope of my contribution to the research presented in this doctoral dissertation.

I conceived the idea and principle aim for this dissertation and the five studies conducted. I developed the study design and protocol for each of the five studies with input from my supervisors and study collaborators.

My contributions to data management were as follows. I assisted with data cleaning, consistency checking and validation of routine TB program data from the Cape Town study setting (Chapter 2 and 3), and record linkage between individual treatment episodes, as well as between treatment episodes and molecular (strain-type DNA) data. I coded and recoded variables for data analysis (Chapters 2, 3, 5 and 6).

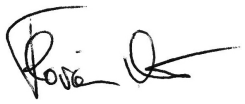
My contributions to the empirical research (Chapters 2,3,5 and 6) were as follows. I conceived, planned and conducted the data analysis for the studies and interpreted the results with feedback and input from my supervisors and collaborators. I wrote the first manuscript drafts. I revised and finalised the manuscripts with contributions from my supervisors and collaborators, and submitted manuscripts for publication (Chapters 2,3,5).

My contributions to the mathematical modeling study (Chapter 4) were as follows. I wrote the study protocol, developed the model structure, collected the data, specified parameter values and calibration targets with input from my supervisors and collaborators. I assisted with model implementation and data analysis. I interpreted the results with input from my supervisors and collaborators. I wrote the first manuscript draft, revised and finalised the manuscript with contributions from my supervisors and collaborators and submitted the manuscript for publication.

With regard to this dissertation, I declare that I wrote the first draft of each chapter. I revised and finalised the dissertation with feedback and input from my supervisors.

Date: 13 October 2017

Signature of the candidate:



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Abstract

Better strategies are needed to reduce *Mycobacterium tuberculosis* (*M.tb*) transmission in tuberculosis (TB) high-incidence settings. Targeting additional control interventions towards groups at highest TB risk may thereby constitute a reasonable approach to make best use of limited resources. One group considered at high TB risk are people with a history of previous TB treatment. In recent years, high rates of recurrent TB after successful TB treatment, frequently due to reinfection with another *M.tb* strain, have been reported from several high-incidence settings. The extent to which previously treated people contribute to the overall TB burden in these settings, and whether control interventions targeted towards this high-risk group could help reduce transmission has not been established.

The aim of the research presented in this dissertation was to characterise the risk of TB among people with a history of previous TB treatment, and to project the impact of control interventions targeted at this subgroup on the trajectory of TB epidemics in high-incidence settings. Towards this aim, I conducted a total of five studies, four of which are based on traditional epidemiological analysis (Chapters 2,3, and 5,6), and one used a transmission-dynamic mathematical model (Chapter 4).

Two studies were based on routine TB program data from a high-incidence setting in suburban Cape Town. The first aimed at estimating the rate of re-treatment for smear-positive TB dependent on whether individuals had completed their previous TB treatment (Chapter 2). For the second, I used *M.tb* strain-type DNA fingerprinting data for a subset of patients re-treated for recurrent smear-positive TB to investigate the relationship between the type of recurrence, i.e. endogenous reactivation (relapse) or exogenous reinfection, and the time to recurrent smear-positive TB (Chapter 3).

I found, among 2,136 smear-positive TB patients, a high rate of re-treatment for smear-positive TB among those who had been lost to follow-up from treatment (6.86 [5.59-8.41] per 100 PYRS). By the end of the second year 28% had been diagnosed again with smear-positive TB. The rate was 3-5-times higher (aHR: 3.97 [3.00 - 5.26]) than after treatment success (cure: 2.09 [1.81-2.41]). Among those who had successfully completed TB treatment, the rate of smear-positive TB was at least 4-times higher than the estimated rate of new smear-positive TB in this setting. Individuals after successful treatment accounted for the majority (68%) of TB patients re-treated for smear-positive TB (Chapter 2).

Exogenous reinfection was the underlying mechanism of disease recurrence in 66 (51%) of 130 individuals re-treated for smear-positive TB after previous treatment success. The proportion did not change after restricting the analysis to individuals with documented HIV-negative test results (27 [51%] reinfections of 53 recurrences). The rate of relapse was highest 4-5 months after treatment completion, whereas the rate of reinfection TB dominated after the first year and remained high for several years (Chapter 3).

I then used a calibrated transmission-dynamic mathematical model to project the population-level impact of interventions targeted at previously treated people in the same high-incidence setting. The interventions modelled were annual targeted active case finding (TACF) and secondary isoniazid preventive therapy (2°IPT) among people who had successfully completed TB treatment. The model projected that, under current control efforts, local TB incidence will remain in slow decline for at least another decade in this setting, and that interventions targeted at previously treated people would greatly accelerate this decline. Annual TACF combined with 2°IPT was projected to avert 40% (20%-59%) of incident TB cases and 41% (16%-62%) of TB deaths estimated to occur in the local population between 2016 and 2025 (Chapter 4).

While the previous 3 studies (Chapters 2-4) had focussed on a particular TB high-incidence setting in suburban Cape Town, I conducted two further studies to explore whether specific characteristics of previously treated TB observed in suburban Cape Town extend to other high-incidence settings in Southern Africa.

I analysed TB prevalence survey data for more than 64,000 adults in 8 South African and 16 Zambian communities, to estimate TB prevalence stratified by history of previous TB treatment, and to investigate the extent to which previously treated people contributed to the overall

prevalent TB burden. The study revealed a high prevalence of bacteriologically-confirmed TB among previously treated people in the 8 South African (overall: 3.81% [95%CI 3.25%–4.47%]) and the 16 Zambian (1.01% [95%CI: 0.65%–1.55%]) communities. Previously treated people accounted for 20.7% and 10.4% of prevalent TB cases in the South African and Zambian communities, respectively, and for more than 20% in 9 of the 24 communities overall (Chapter 5).

Finally, I made use of electronic TB register data from the 52 South African health districts to investigate the proportion of previously treated individuals among notified TB patients treated for bacteriologically-confirmed TB in 2011. The study showed that the proportion of previously treated TB varied in the 52 health districts between 7.6% and 40%. The proportion exceeded 20% in 17 of the 52 districts. Higher proportions of previously treated TB correlated with higher TB case notification rates ($r=0.75$; $P<0.001$) and lower estimates of HIV prevalence ($r=-0.45$; $P<0.001$) in the districts (Chapter 6).

In conclusion, this research documents high rates of TB after previous loss to follow-up from treatment and after treatment success in a high-incidence setting. People who previously completed TB treatment constitute the majority of smear-positive TB re-treatment patients, suggesting that efforts to ensure treatment adherence alone are unlikely to be sufficient to reduce the TB burden among previously treated people. Our study is consistent with earlier findings from this setting that reinfection contributes considerably to recurrent TB, even among HIV-uninfected individuals. I document for the first-time distinct temporal dynamics of relapse and reinfection TB. These dynamics suggest that sampling bias/differences in follow-up time is likely to explain the substantial variation in the contribution of reinfection to disease recurrence reported in observational studies. High rates of reinfection TB over a lengthy time after treatment completion suggest that the performance of TB treatment alone is unlikely to explain the high burden of recurrent TB in this setting.

I used a transmission-dynamic mathematical model to address the idea of a targeted control strategy at a time when novel strategies are urgently needed to reduce transmission and the TB burden in populations most severely affected by TB. The model suggests considerable public health potential for TB control interventions targeted at previously treated people in this high-incidence setting. I identified several other high-incidence communities (and districts) where previously treated individuals contribute considerably to the prevalent and incident (notified) TB burden, and where interventions in this high-risk group might be relevant. This work represents only a first step towards evaluating the potential of this targeted control approach. Further research will be necessary to determine the feasibility, impact and cost-effectiveness of targeting interventions towards previously treated people for reducing transmission and the TB burden in high-incidence settings.

Opsomming

Beter strategieë word vereis om die oordrag van *Mycobacterium tuberculosis* (*M.tb*) in omgewings met 'n hoë tuberkulose (TB) insidensie te verminder. Die toespitsing van bykomende beheerintervensies op groepe met die hoogste TB-risiko kan dus'n redelike benadering wees om beperkte hulpbronne so doeltreffend moontlik te benut. Een groep wat as hoë TB-risiko beskou word, is persone met 'n geskiedenis van vorige TB-behandeling. Die afgelope paar jaar is 'n groot aantal gevalle van wederkerende TB ná suksesvolle TB-behandeling, dikwels as gevolg van herinfeksie met 'n ander M.tb-stam, in verskeie hoë-insidensieomgewings aangemeld. Die mate waarin voorheen behandelde persone tot die algehele TB-las in hierdie omgewings bydra, en of beheerintervensies met die oog op hierdie hoë-risikogroep oordrag kan help verminder, is nog nie vasgestel nie.

Die doel van die navorsing wat in hierdie proefskrif aangebied word, was om die TB-risiko onder persone met 'n geskiedenis van vorige TB-behandeling te beskryf, en om te voorspel watter impak beheerintervensies onder hierdie subgroep op die trajek van TB-epidemies in hoë-insidensieomgewings sal hê. Vir dié doel het ek altesaam vyf studies onderneem, waarvan vier op tradisionele epidemiologiese ontleding (hoofstuk 2, 3, 5 en 6) en een op 'n dinamiese wiskundige oordragmodel berus (hoofstuk 4).

Twee studies was gegrond op roetine TB-programdata uit 'n hoë-insidensieomgewing in voorstedelike Kaapstad. Die doel van die eerste studie was om die herbehandelingskoers vir smeerpositiewe TB te bepaal na gelang van of individue hulle vorige TB-behandeling voltooi het (hoofstuk 2). Vir die tweede studie het ek M.tb-stamtipe DNS-vingerafdrukdata gebruik van 'n subgroep pasiënte wat opnuut vir wederkerende smeerpositiewe TB behandel is om die verwantskap tussen die tipe wederkerende TB – d.w.s. endogene heraktivering (relaps) of eksogene herinfeksie – en die tydverloop tot en met wederkerende smeerpositiewe TB te bepaal (hoofstuk 3).

Ek het bevind dat uit 'n groep van 2136 smeerpositiewe TB-pasiënte was die herbehandelingskoers vir smeerpositiewe TB hoog onder diegene wat hulle opvolg van behandeling nagelaat het (6,86 [5,59-8,41] per 100 PJ). Teen die einde van die tweede jaar was 28% reeds weer met smeerpositiewe TB gediagnoseer. Die koers was drie tot vyf keer hoër (aHR: 3,97 [3,00-5,26]) as ná behandelingsukses (genees: 2,09 [1,81-2,41]). Onder diegene wat hulle TB-behandeling suksesvol voltooi het, was die smeerpositiewe TB-syfer ten minste vier keer hoër as die geskatte nuwe smeerpositiewe TB-syfer in hierdie omgewing. Individue wat voorheen suksesvol behandel is, het die meerderheid (68%) uitgemaak van TB-pasiënte wat weer vir smeerpositiewe TB behandel is (hoofstuk 2).

Eksogene herinfeksie was die onderliggende meganisme van wederkerende siekte by 66 (51%) uit 130 individue wat ná vorige suksesvolle behandeling weer vir smeerpositiewe TB behandel is. Die gedeelte het onveranderd gebly selfs nadat die ontleding beperk is tot individue met gedokumenteerde MIV-negatiewe toetsresultate (27 [51%] herinfeksies uit 53 gevalle van wederkerende siekte). Die relapssyfer was die hoogste sowat vier tot vyf maande na die voltooiing van behandeling, terwyl die TB-herinfeksiesyfer 'n hoogtepunt bereik het na die eerste jaar, en vir 'n hele aantal jaar daarna hoog gebly het (hoofstuk 3).

Daarna het ek 'n gekalibreerde dinamiese wiskundige oordragmodel gebruik om die populasievlakimpak van intervensies vir voorheen behandelde persone in dieselfde hoë-insidensieomgewing te voorspel. Die gemodelleerde intervensies was jaarlikse toegespitste aktiewe gevalleopsporing ("TACF") en sekondêre isoniasied-voorkomingsbehandeling ("2°IPT") onder persone wat TB-behandeling suksesvol voltooi het. Die model dui daarop dat, met huidige beheerpogings, plaaslike TB-insidensie in hierdie omgewing vir minstens nog 'n dekade stadig sal daal, en dat intervensies met die oog op voorheen behandelde persone dié daling beduidend sal versnel. Volgens die model sal jaarlikse TACF in samehang met 2°IPT sowat 44% (20-59%) van nuwe TB-gevalle en 41% (16-62%) van TB-sterftes verhoed wat na raming tussen 2016 en 2025 in die plaaslike populasie sal voorkom (hoofstuk 4).

Terwyl die drie studies hierbo (hoofstuk 2-4) op 'n bepaalde voorstedelike Kaapse omgewing met 'n hoë TB-insidensie gekonsentreer het, het ek ook twee verdere studies gedoen om te

bepaal of sekere kenmerke van voorheen behandelde TB wat in voorstedelike Kaapstad opgemerk word, ook in ander hoë-insidensieomgewings in Suider-Afrika voorkom.

Hiervoor het ek TB-prevalensieopnamedata van meer as 64000 volwassenes in agt Suid-Afrikaanse en 16 Zambiese gemeenskappe ontleed om TB-prevalensie na gelang van vorige TB-behandelingsgeskiedenis te beraam, en om vas te stel in watter mate voorheen behandelde persone tot algehele TB-prevalensie bydra. Die studie dui op 'n hoë prevalensie van bakteriologies bevestigde TB onder voorheen behandelde persone in die agt Suid-Afrikaanse (algeheel: 3,81% [95%CI 3,25-4,47%]) sowel as die 16 Zambiese gemeenskappe (1,01% [95%CI: 0,65-1,55%]). Voorheen behandelde persone maak onderskeidelik 20,7% en 10,4% van TB-prevalensie in die Suid-Afrikaanse en Zambiese gemeenskappe uit, en meer as 20% in nege van die 24 gemeenskappe altesaam (hoofstuk 5).

Laastens het ek elektroniese TB-registerdata van die 52 Suid-Afrikaanse gesondheidsdistrikte gebruik om die persentasie voorheen behandelde individue te bepaal onder aangemelde TB-pasiënte wat in 2011 vir bakteriologies bevestigde TB behandel is. Hierdie studie toon dat die persentasie voorheen behandelde TB in die 52 gesondheidsdistrikte tussen 7,6% en 40% wissel. In 17 van die 52 distrikte oorskry die persentasie 20%. Hoër persentasies voorheen behandelde TB korreleer met hoër TB-aanmeldingsyfers ($r = 0,75$; $P<0,001$) en laer MIV-prevalensieskattings ($r = -0,45$; $P<0,001$) in die distrikte (hoofstuk 6).

Ten slotte bevind hierdie navorsing hoë TB-syfers ná vorige verlies van opvolg tydens behandeling sowel as ná suksesvolle behandeling in 'n hoë-insidensieomgewing. Persone wat voorheen TB-behandeling voltooi het, maak die meerderheid uit van smeerpositiewe TB-herbehandelingspasiënte wat daarop dui dat pogings om slegs behandelingsgetrouheid te verseker waarskynlik nie voldoende is om die TB-las onder voorheen behandelde persone te verminder nie. Ons studieresultate strook met vroeëre bevindinge in hierdie omgewing dat herinfeksie beduidend tot wederkerende TB bydra, selfs onder MIV-negatiewe individue. Ek dokumenteer ook vir die eerste keer die tyddimensies van TB-relaps en -herinfeksie. Hierdie dimensies dui daarop dat sydigheid in steekproefneming/tydverskille in die duur van opvolg waarskynlik die aansienlike variasie in die bydrae van herinfeksie tot wederkerende siekte in waarnemingstudies verklaar. Hoë TB-herinfeksiesyfers oor 'n lang tydperk ná voltooiing van behandeling dui daarop dat TB-behandelingsprestasie alleen waarskynlik nie die hoë las van wederkerende TB in hierdie omgewing verklaar nie.

My gebruik van 'n dinamiese wiskundige oordragmodel om die gedagte van 'n toegespitste beheerstrategie te ondersoek, val saam met 'n dringende behoefte aan nuwe strategieë om TB-oordrag en die TB-las te verminder by populasies wat die ergste deur dié siekte geraak word. Die model dui op aansienlike openbaregesondheidspotensiaal vir TB-beheerintervensies wat op voorheen behandelde persone in hierdie hoë-insidensieomgewing gerig is. Ek identifiseer ook verskeie ander hoë-insidensiegemeenskappe (en -distrikte) waar voorheen behandelde individue beduidend tot TB-prevalensie en aangemelde TB-insidensie bydra, en waar intervensies vir hierdie hoë-risikogroep moontlik relevant kan wees. Tog is hierdie werk maar die eerste stap om die potensiaal van hierdie toegespitste beheerbenadering te beoordeel. Verdere navorsing word vereis om die haalbaarheid, impak en kostedoeltreffendheid van toegespitste intervensies vir voorheen behandelde persone te bepaal in die strewe na laer TB-oordrag en 'n kleiner TB-las in hoë-insidensieomgewings.

Chapter 1: Introduction

1.1. Epidemiology and control of tuberculosis

1.1.1. Determinants of exposure, infection and disease

Tuberculosis (TB) is an air-borne communicable disease caused by *Mycobacterium tuberculosis* (*M.tb*). Despite progress in TB control, the disease remains a major challenge to global public health. At present time, nearly a quarter of the world's population is estimated to be infected with *M.tb* [1].

A set of key factors determine the occurrence and distribution of TB in populations. Knowledge about these factors has guided important principles in TB control. The determinants (and risk factors) of TB can be divided into three main groups, those of (I) exposure to *M.tb*, (II) infection with *M.tb* given exposure, and (III) progression to TB disease given infection.

During ***exposure***, human-to-human transmission may occur via the inhalation of bacteria-containing micro-droplets, so called "droplets nuclei" [2], which are expectorated by infectious individuals and inhaled by the person becoming infected. Whether a person becomes exposed to *M.tb* is determined by (i) the number of individuals who develop TB in a given population, (ii) their average degree and duration of infectiousness, and (iii) the rate at which an infectious person contacts susceptible individuals in this population. The latter, the rate of contact, is highly variable within and between populations as it depends on the type of relationships between individuals, their age, as well as social and cultural norms and habits [3].

The probability of ***infection*** is expected to vary considerably on an individual level. Two main determinants condition whether an individual becomes infected given exposure. (i) The dose (quantity) of *M.tb* that is inhaled depends on the infectiousness of the index case (i.e. the person transmitting) and the proximity and duration of contact. The former, the infectiousness of the index case, is dependent on the site and extent of TB disease as well as the capability of the index case to produce and expectorate bacteria-containing droplets nuclei in the air. Transmission usually occurs by means of coughing, less frequently via sneezing, speaking or singing. Proximity and duration of contact to an infectious TB index case may increase the infectious dose of *M.tb* during exposure. Finally, environmental factors, such as air circulation, ventilation and ultraviolet light radiation (e.g. through sunlight) may influence the concentration of droplets nuclei in the inhalable air. (ii) Secondly, host immune-defence mechanisms determine the risk of becoming infected. The immunological correlate of *M.tb* infection is a specific T-cell immune response. After inhalation, the bacteria reach the lower airways and survive in alveolar macrophages through preventing apoptosis. Antigens of *M.tb* are then presented to T-cells by dendritic cells migrating to lymph nodes, and T-cell memory is being created as a prerequisite for T-cell immunity. Innate mechanisms of immune defence may act before infection occurs. These mechanisms include the mucociliary clearance in the upper respiratory tract which may help to clear out *M.tb* before infection. Furthermore, variability in the function of alveolar macrophages in killing *M.tb* is expected to influence the probability of infection.

Progression to TB disease may occur within weeks of months after infection or upon reactivation of latent infection. Latency may last lifelong. The risk of disease progression is determined by a variety of factors that modulate immunity and the capability of the immune system to effectively contain *M.tb* infection. These factors include (i) age, (ii) genetic factors, (iii) environmental and lifestyle factors such as smoking, alcohol and substance abuse, and malnutrition, (iv) concomitant (immunocompromising) medical conditions such as human immunodeficiency virus (HIV) infection, diabetes mellitus, silicosis, malignancies, and renal failure (v) immunosuppressive therapy, (vi) pregnancy, and (vii) bacteria-related factors such as strain-virulence and the infectious dose. Disease progression may occur upon reinfection with *M.tb*. However, prior (distant) latent infection is associated with a lower risk of disease progression [4].

The substantial individual-level variability in factors determining exposure, infection and disease explains the considerable degree of heterogeneity in *M.tb* transmission and the distribution of TB that is observed within and between populations and constitutes a major challenge for reducing TB morbidity and mortality worldwide.

1.1.2. Global TB incidence and mortality

In 2015, an estimated 10.4 million incident cases of TB occurred globally (uncertainty range: 8.7-12.2 million) [5]. Of these, 6.4 million (62%) were male and 4.0 million (38%) were female, and nearly 1.0 million (9.6%) of all were children.

Of all incident TB cases, an estimated 1.2 million (11%) occurred among people living with Human Immunodeficiency Virus (HIV) infection, 71% of these in countries of the World Health Organization (WHO) African Region. Here, almost one-third (31%) of incident TB cases was estimated to be co-infected with HIV [5].

Globally, 0.58 million (5.6%) incident TB cases were estimated to suffer from rifampicin- or multidrug-resistant (RR/MDR-) TB. The estimated prevalence of RR/MDR-TB among new and previously treated TB cases was 3.9% and 21%, respectively [5].

The number of incident TB cases occurring globally in 2015 was equivalent to 142 (119 - 166) per 100,000 population. Estimates of TB incidence vary considerably among countries worldwide. Countries with a relatively high TB incidence rate thereby account for a considerable fraction of the (absolute) number of incident TB cases worldwide. For example, in 2015, there were 28 countries with a TB incidence rate estimated to be more than twice the global TB incidence rate (range: 306 - 824 per 100,000 population). These 28 countries had a total population of 0.94 billion and accounted for 35% of the incident TB burden globally (Figure 1.1). Eighteen of these 28 high-incidence countries are located in the World Health Organization (WHO) African, 6 in the South-East Asian and 6 in the Western-Pacific Region.

Both, the estimated TB burden and TB incidence have been slowly declining at global level over the past years. The annual rate of decline in TB incidence was 1.4% per year between 2000 and 2015. This slow decline is now observed in most parts of the world [5].

In 2015, only about 6.15 million people* with an incident episode of TB were notified through national TB control programs (NTPs) in 2015, representing 59% of the total number of estimated incident TB cases. Of these, about 5.68 million (92%) were new and 0.48 million (7.7%) were relapse† cases. Of notified new and relapse cases, approximately 5.23 million were pulmonary TB cases, 3.00 million (57%) of whom were bacteriologically confirmed by any method, and 0.97 million were cases of extra-pulmonary TB [5]. In addition to new and relapse cases a total of 228,700 TB cases worldwide were re-notified after having been previously diagnosed with TB but re-treated after unfavourable or unknown treatment outcome.

TB is one of the top 10 causes of death worldwide. An estimated 1.8 million people died from TB in 2015, including 0.4 million TB deaths among people living with HIV infection. The global case fatality ratio‡ was 17% and varied considerably worldwide, exceeding 20% especially in countries with high HIV prevalence [5].

* Numbers of TB cases in this section are rounded to the second decimal place.

† The World Health Organization recording and reporting system considers as "relapse" any TB case with a history of previous treatment success without discriminating between true relapse and reinfection TB.

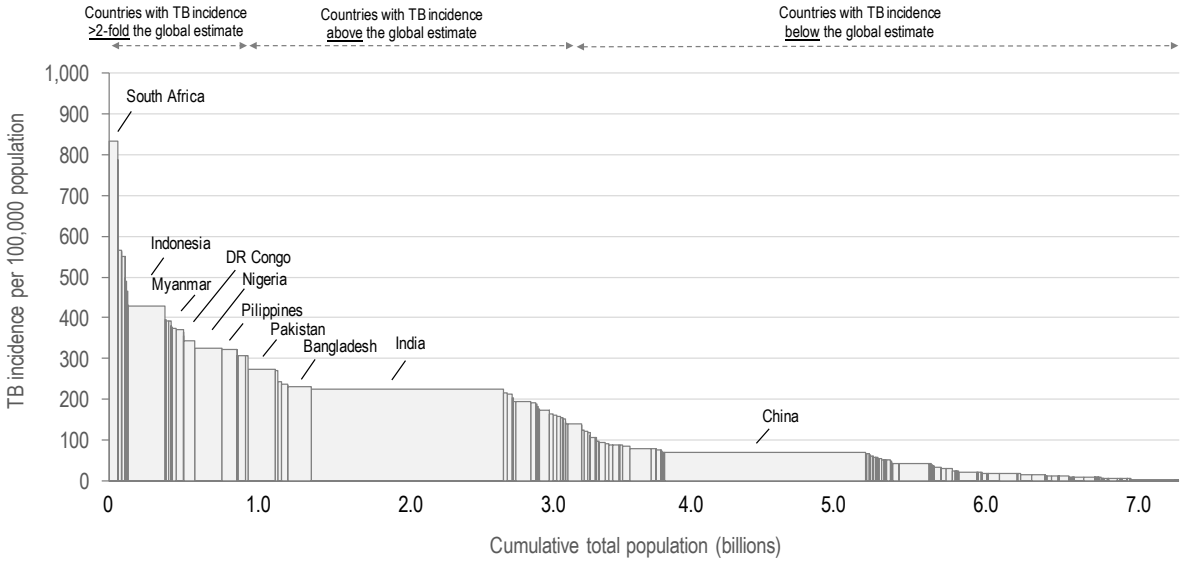

Figure 1.1. Global distribution of estimated TB incidence rates vs. total population in 217 countries worldwide, 2015. (The area of the bars is proportional to the total number of incident TB cases.) Labelled are the top 10 countries by absolute numbers of incident TB cases (data source: WHO Global TB Database)

1.1.3. History and principles of TB control

Following a resurgence of TB in many parts of the world, the World Health Organization (WHO) had declared TB a global emergency in 1994 [6]. The need for increased and coordinated efforts to tackle the global burden of TB had eventually been recognised, and in 1996, a strategy for global TB control had been initiated.

This new global strategy became known as the *Directly Observed Treatment Short-course (DOTS) Strategy* and emphasised primarily on finding and detecting infectious TB cases and treating them with the internationally-approved standardised 6-8 months ("short-course") TB treatment regimen. To ensure patient compliance, the WHO promoted directly observed treatment (DOT), during which patients were to be observed by health-care staff while taking their medication. Passive case detection was recommended because more intensified case finding measures in populations were expected to require considerable resources and to be less cost-effective.

The main priority in the initial phase of the global TB control strategy had been to find and treat new and most infectious (smear-positive) TB cases. Smear-microscopy was the preferred diagnostic tool because it was relatively easy to implement in low-resource settings, results were relatively quickly available, and microscopy was sensitive enough to identify the most infectious TB cases. Less emphasis had been on TB among previously treated people [7] and clinically-diagnosed (smear-negative) TB cases. Recording and reporting and monitoring of treatment outcomes among new smear-positive TB cases formed an essential part of the *DOTS Strategy*. The strategy also included measures to ensure sustained political and financial commitment and regular drug supply in the countries.

A primary goal of the *DOTS Strategy* was the prevention of transmission globally through finding and treating infectious TB. Smaller emphasis was made on prevention of progression among people already infected with *M.tb*. Preventive therapy had been recommended only for selected high-risk groups including exposed children less than 5 years of age and people living with HIV.

At the beginning of the new millennium, the WHO modified and renamed the *DOTS Strategy.* The new *Stop TB Strategy* aimed to "dramatically reduce the global burden of TB by the year 2015 in line with the Millennium Development Goals" [8].

Targets for global TB control were agreed, and a global plan to *Stop TB 2001 – 2005* was developed and update twice, for 2006-2010 and for 2011-2015, to ensure progress in global TB control. Expansion of TB case detection and DOT remained central to global TB control

activities. However, the *Stop TB Strategy* between 2001 and 2015 aimed at addressing more effectively the specific challenges of TB control [8].

In response to the dramatic burden of HIV-associated TB worldwide, efforts have been made to strengthen TB and HIV collaborative activities in the countries, for example by strengthening HIV counselling, testing and treatment among TB patients, and by promoting intensified TB case finding, infection control and preventive therapy among people living with HIV [9]. Early initiation of antiretroviral treatment (ART) among TB patients living with HIV was found to be save and to improve survival [10] and is now recommended universally.

Capacity for sputum smear microscopy and *M.tb* culture has been expanded globally to strengthen the detection of TB cases. Novel molecular and more rapid diagnostic tools such as the *Xpert MTB/RIF* [11] and the *Genotype MTBDR Line Probe Assay* [12] have been approved and are currently being rolled out. The initial focus on diagnosing the most infectious TB cases has been changed toward diagnosing all TB cases, regardless of bacteriology or treatment history [7]. Particular efforts have been made to strengthen the diagnosis and treatment of TB among children. Treatment outcomes are now being monitored among all new and relapse TB cases, regardless of bacteriological confirmation.

The Stop TB Strategy has also aimed to respond more effectively to the emerging global burden of RR/MDR-TB. Higher coverages of drug-susceptibility testing (DST) among previously treated TB cases, more recently also among new TB cases, have been promoted. Efforts to scale up treatment of RR/MDR-TB and extensively drug-resistant (XDR-) TB along with monitoring of treatment outcomes have been strengthened.

Last but not least, the *Stop TB Strategy* has put particular emphasis on promoting research and innovation, particularly for the development and roll-out of novel diagnostic tools, the discovery of new TB drugs and of a new TB vaccine.

1.1.4. Current progress and challenges

Considerable progress has been made in global TB control in the past two decades. Between 2000 and 2015, more than 84 million people with an incident episode of TB had access to quality TB treatment under NTPs globally.[*] During this time, TB treatment was estimated to have averted 39 million deaths among HIV uninfected people, and, supported with antiretroviral treatment (ART), an additional 9.6 million deaths among people living with HIV [5]. Treatment success among TB patients treated in 2014 was high at 83% [5]. In 2015 the world was estimated to have reached the global Stop TB strategy targets of reducing TB prevalence and mortality by 50% relative to 1990 [13]. Global TB incidence has been reversed and is now declining by an average 1.4% annually since the year 2000 [5].

Despite the considerable progress made in the past two decades, global TB control currently faces serious challenges. Currently, only 60% of incident TB cases are estimated to have access to quality TB treatment [14], leaving a case detection (and treatment) gap of approximately 4 million people every year [5]. Progress in case detection and treatment is threatened by weak health-care systems and a considerable lack of funding [5]. Global progress in increasing the coverage of DST and scaling up treatment for RR/MDR-TB and XDR-TB has been slow and unevenly distributed [5].The lack of more effective drugs and regimens to treat drug-resistant TB poses a serious challenge in many countries. Furthermore, failure to scale up interventions to prevent TB in high-risk populations, especially among children, people living with HIV and those living with diabetes threatens progress in TB control especially in TB-endemic settings. All these challenges have contributed to a global pace in TB control that is slower than previously expected [15]. The decline in TB incidence currently remains insufficient in many parts of the world. TB continues to be among the top 10 leading causes of death among people worldwide.

To address these challenges, and to significantly increase the pace in global TB control, an ambitious new strategy has been launched in 2015 [16]. The WHO-endorsed *End TB Strategy* [16] was developed in line with the United Nations *Sustainable Development Goals* (Goal 3:

[*] Globally, a total of 84,171,425 new and relapse TB cases were notified to the WHO between 2000 and 2015. (Source: WHO global tuberculosis database, available from: www.who.int/tb/data)

"Good Health and Well-being") [17] and promises no less than a paradigm shift, from "stopping" TB to eliminating the disease globally by the end of 2035. The strategy includes specific milestones and targets towards the year 2035. The key targets for 2035 are to (I) reduce the global TB incidence rate by 90% to less than 10 incident cases per 100,000 population, (II) reduce the absolute number of TB deaths by 95% relative to 2015, and (III) ensure that no TB-affected families face so-called "catastrophic costs" due to TB. To achieve these ambitious targets, a global investment plan for specific measures to fight TB worldwide has been developed. Integrated and patient-centred care and prevention are at the core of the *End TB Strategy*. This includes measures to ensure universal drug-susceptibility testing, screening of contacts of TB patients and of TB high-risk groups, TB treatment and patient support, management of HIV and co-morbidities, as well as preventive treatment and vaccination for people at high TB risk. Progress is to be ensured by "bold policies and supportive systems" as well as "intensified research and innovation" [16].

1.1.5. TB epidemiology and control in South Africa

TB is currently a major threat to public health in South Africa, a country with a total population of 54 million people, more than half of whom are living in poverty [18]. South Africa currently ranks sixth among countries worldwide in terms of absolute numbers of incident TB cases. In 2015, there were an estimated 454,000 (294,000 - 649,000) incident TB cases, of whom 263,000 (58%) were male, 191,000 (42%) were female, and 33,000 (7.3%) of all were children [19].

Among countries worldwide, South Africa has the highest estimated TB incidence rate, 834 (539 - 1,190) per 100,000 population in 2015 [19], a rate that is six times higher than the global TB incidence rate. Estimates of TB incidence at sub-country level do not exist. However, heterogeneity in reported TB case notification rates, for example, between 413 and 1,095 per 100,000 population in the nine South African Provinces in 2012 [20], suggests that TB incidence may vary substantially in different parts of the country.

A major determinant of TB incidence in South Africa is the concurrent HIV epidemic. The rapid rise in TB incidence that had been observed in South Africa in the mid- to late 1990s was attributed mainly to the concurrent HIV epidemic [21, 22]. In 2015, an estimated 7.0 (6.7 - 7.4) million people in the country were living with HIV infection, equivalent to 13% (12% - 14%) of the total population [23]. People living with HIV constituted 57% (52% - 61%) of incident TB cases [5] and also account for the vast majority TB deaths in South Africa (74%) of 98,000 in 2015) [19].

The estimated TB incidence among people living with HIV was 3,766 per 100,000 people in 2015, several-fold higher than TB incidence in the total population (Figure 1.2).* Although TB incidence among HIV-uninfected people was relatively lower (411 per 100,000 people), this rate was still very high by international comparison, e.g. more than twice the global TB incidence rate.

* Incidence rates shown are based on estimated numbers of TB cases among HIV-infected people published in the Global TB Report 2016 and UNAIDS estimates of HIV prevalence in the population.

An additional challenge for TB control in South Africa is the emergence of drug-resistant *M.tb* strains. A recent drug-resistance survey found a prevalence of RR-/MDR-TB of 3.4% (2.5% - 4.3%) among notified new and 7.1% (4.8% - 9.5%) among previously treated TB cases [24]. In 2015, there were an estimated 20,000 (13,000 - 27,000) incident cases of RR-/MDR-TB in the country, equivalent to 37 (24 – 50) per 100,000 people [19]. Recent reports of nosocomial and community transmission of MDR and extensively drug-resistant *M.tb* have raised concerns of rising drug-resistant TB in the country [25-27].

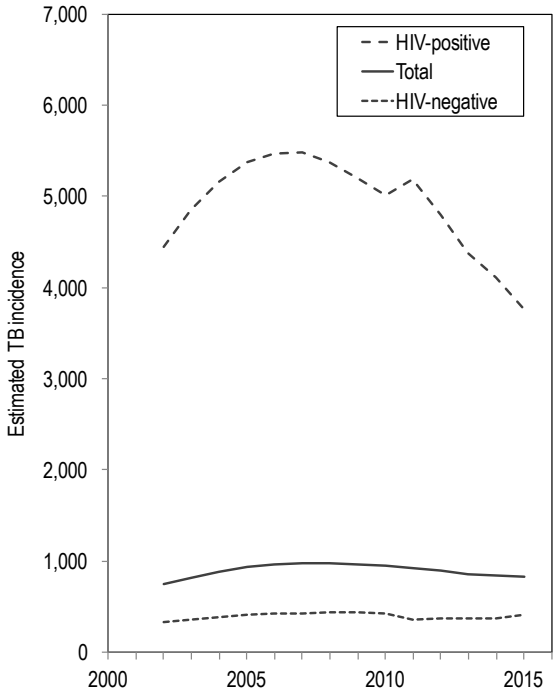

Figure 1.2: Estimates of TB incidence in South Africa 2002-2015, overall and stratified by HIV infection. HIV-stratified rates are based on UNAIDS estimates of HIV prevalence in the population.

Increased efforts have been made over the past two decades in South Africa to respond more effectively to the TB epidemic while also tackling the major burden of HIV. The DOTS strategy was introduced in 1996, and directly-observed standard TB treatment has since been available country-wide [28]. In 2003, TB had been declared a national emergency in South Africa, and a national crisis plan was developed [21]. An electronic TB recording and reporting system was implemented in 2003 [21]. In 2007, guidelines for enhancing *M.tb* infection control in the country were published. National guidelines for TB control were developed in 2008 and revised in 2014. Since 2010, the country has substantially scaled up measures to expand ART and isoniazid preventive therapy (IPT) among people living with HIV [29]. In 2011, the rapid molecular test Xpert MTB/Rif was introduced and is now routinely used as a primary bacteriological test for TB, as a replacement for sputum smear microscopy.

The steep increase in TB incidence in South Africa observed since the late 1990s has now been halted and began to reverse in 2008. TB incidence has since been declining by an average 2.1% annually. The reversing trend in TB incidence is attributable mainly to a decline in TB incidence among people living with HIV (Figure 1.2) which has been related to the scale up in ART coverage in the country [20]. Annual TB incidence rates have been declining in the past five years by an average 1.9% annually. Nevertheless, under current control efforts, progress in tackling the TB epidemic in the country remains limited. TB incidence currently still doubles the rate estimated in the early 1990s. Even if the current pace of decline in TB incidence can be sustained, declines in TB incidence in the forthcoming years will be moderate compared to the emergence of TB about two decades ago, and insufficient to reach the milestones and targets of the *End TB Strategy* (Figure 1.3).

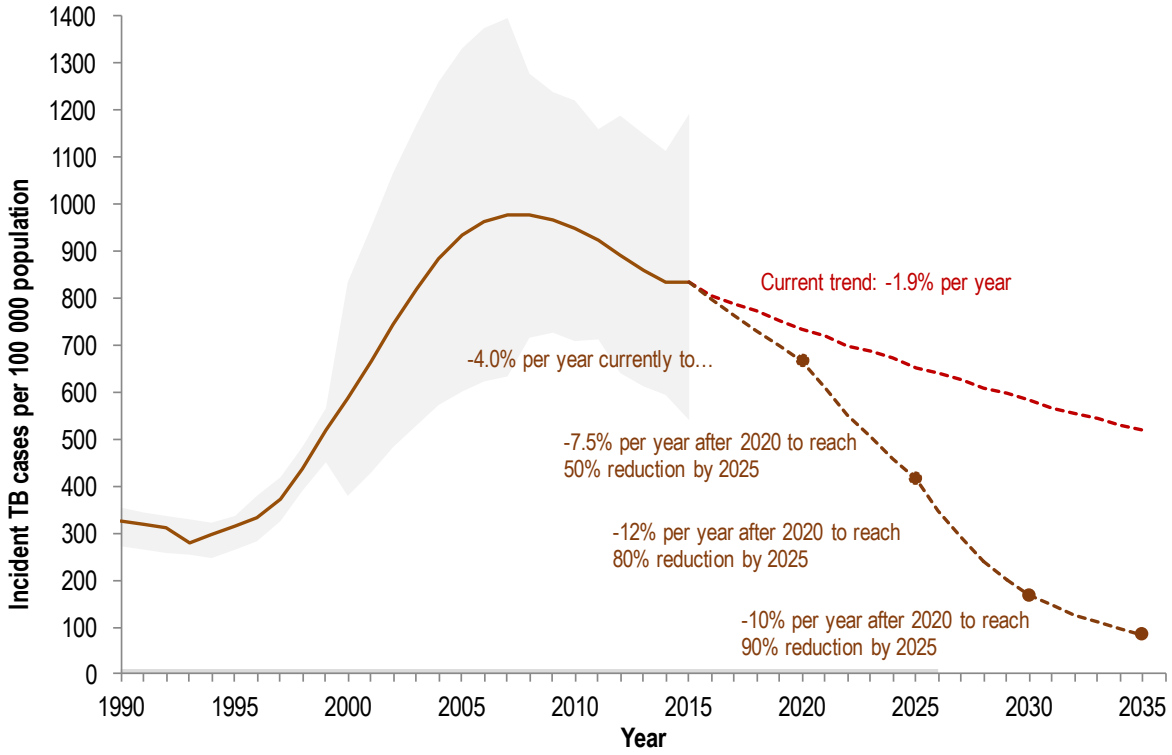

Figure 1.3. TB incidence in South Africa: trends 1990-2015 estimated by the WHO, and projections under the global *End TB Strategy* scenario 2016-2035; grey shaded areas represent uncertainty intervals (Source: own [unpublished] projections using data from the WHO Global TB control program)

1.2. Enhancing TB control in high-incidence settings

1.2.1. Specific challenges of TB control in high-incidence populations

Substantial progress in global TB control is necessary to achieve the milestones and targets set out by the *End TB Strategy*. This progress is threatened particularly by the limited success in reducing transmission and the TB burden in countries and settings with a high incidence of TB. The reasons why TB incidence remains high in these settings are complex and vary from setting to setting. However, the following key characteristics apply to most of these settings. They explain why conventional TB control is currently failing, and why additional and enhanced efforts are required to effectively reduce TB.

- TB high-incidence populations often include larger numbers of individuals at increased susceptibility to *M.tb* infection and disease. Risk factors that are more commonly observed in these populations and that promote TB susceptibility include mal- and inadequate nutrition [30], and harmful lifestyles such as smoking, alcohol [31] and substance abuse. Frequent concomitant diseases and conditions, most of all HIV infection and diabetes [32], increase the susceptibility to TB in these populations. Environmental and occupational hazards such as indoor air-pollution or silica dust exposure may increase susceptibility of TB. Furthermore, observations of high TB incidence in indigenous populations support the hypothesis that host genetic factors in populations may determine susceptibility and resistance to TB, although studies have been struggling to discriminate between the effect of genetic variability and environmental (including poverty-associated) risk factors in these populations.
- Delay in detecting and treating TB is common in high-incidence settings. Observational studies report a high prevalence of untreated TB from different settings [33-35],

suggesting that TB control programs which currently rely exclusively on passive case finding may fail to promptly identify and treat TB cases [36]. Infectious individuals may remain in in the communities for several months before being detected and treated for TB [37]. Underlying reasons for this delay include individual barriers to accessing TB care such as T-related stigma and lack of knowledge as well as financial constraints and lack of transport to access care. Individuals may also be diagnosed with TB but not initiate TB treatment (initial loss to follow-up [38]). Furthermore, health-system constraints, for example a lack of qualified personnel, insufficient patient triage and referral systems, lack of laboratory capacity and diagnostic delay, may impose additional barriers for prompt diagnosis and treatment of TB.

- Both, the high number of people developing TB and the delay in detecting and treating infectious individuals result in high rates person-to-person transmission of M.tb [39], a major challenge to TB control in high-incidence settings [39]. Overcrowding [40] and high contact rates as well as the lack of infection control measures, for example in health-care facilities, prisons, occupational settings and public transport, may generate “hotspots” of sustained *M.tb* transmission in high-incidence settings. Failure to adequately treat and cure TB patients, especially those suffering from MDR-TB and XDR-TB, may further aggravate the risk of transmission in these settings [27, 41].
- Finally, TB was and remains closely linked with poverty [42, 43]. Poverty amplifies and aggravates all of the above characteristics and therefore constitutes a key underlying challenge to reduce TB in high-incidence settings.

1.2.2. Population-based TB control interventions in high-incidence settings

Several strategies and interventions have been suggested to directly confront the specific challenges of TB control in high-incidence populations. These include efforts to (i) prevent infection or disease progression and (ii) enhancing TB case finding / reducing diagnostic and treatment delay.

Prevention through vaccination would be a suitable strategy, but effective vaccines to significantly reduce TB incidence in high-incidence populations are currently unavailable. *Bacille Calmette-Guérin* (BCG) vaccination at birth, in consideration of HIV status, is already common practice in many countries, based on evidence that the vaccine protects against severe disease (such as meningeal or military TB) in children. However, vaccine efficacy trials have shown considerable heterogeneity in the protective effect of BCG in adults. The protective effect of BCG appears incomplete especially against pulmonary TB, the most common form of TB worldwide, suggesting that the scale up of BCG coverage would have limited impact on disease control especially in high-incidence settings were repeated exposure and reinfection is more likely. Novel and more effective vaccines are currently under development, but an alternative vaccine to complement or replace BCG in high-incidence settings is currently not available.

More aggressive use of isoniazid preventive therapy (IPT) is currently being considered as a strategy for reducing TB in high-incidence populations. A recent cluster-randomised trial of mass-IPT in a mining population in South Africa [44] showed that although IPT was protective on an individual level, the intervention had no effect on TB in the (cluster) population, presumably because the protective effect of IPT was lost shortly after cessation of treatment [45]. The use of at least 6 to 9 months of IPT is currently recommended for people living with HIV [46]. Feasibility and cost-implications as well as the risk of selection and emergence of drug-resistant *M.tb* strains [47, 48] have been issued as major concerns against more long-term and population-wide use of IPT in high-incidence populations.

Intensifying TB case detection through active or enhanced TB case finding are being considered as a means of reducing delay in diagnosing and treatment of infectious individuals as a means of reducing transmission [49]. Active TB case finding (ACF) in populations may be conducted either during household visits or upon invitation of people to mobile screenings. Data about the impact of ACF in high-incidence populations remain limited to date; the individual- and community-level benefits of ACF are thus uncertain [50].

Only one recent community-randomised trial in southern Africa has looked at the population-level impact of ACF. During this trial, consecutive six-monthly ACF via a mobile van and door-to-door visits led to a 41% decrease in TB prevalence in a high-incidence population in Zimbabwe [51]. Another large community-randomised trial of ACF in South Africa is expected to be completed in 2019 [52]. Enhanced TB case finding (ECF) is possible, for example, through community mobilisation or through enhancing access to TB diagnostics [53]. However, results from the Zambia South Africa AIDS and Tuberculosis Reduction (ZAMSTAR) trial, a large randomised intervention trial in 24 high-incidence communities in South Africa and Zambia, suggested that enhanced TB case finding did not reduce the number of new *M.tb* infections and TB prevalence at the community-level [54].

All of these additional strategies of TB preventions and case finding require large-scale, population-based interventions that demand considerable investments and human resources. Their implementation, in addition to conventional TB control, may be difficult because resources are generally limited and most high-incidence countries are facing severe economical and logistical challenges. These implementation challenges and the considerable uncertainty around epidemiologic impact have tempered enthusiasm in recent years about the use and usefulness of population-wide interventions for reducing TB in high-incidence settings.

1.2.3. Targeting TB control toward high-risk groups

Targeting preventive and case-finding interventions toward specific population subgroups may constitute an attractive strategy for enhancing TB control in high-incidence settings. Such targeted interventions may be more efficient and cost-effective than untargeted interventions if they are focussed directly on subgroups at high TB risk (and those at high risk of transmitting) and thus make better use of resources for TB control.

Figure 1.4 illustrates *direct* and *indirect effects* of a targeted preventive intervention in a population using counterfactual scenarios (intervention vs. baseline scenario). Individuals belonging to the target group may directly benefit from the preventive intervention. This *direct effect* is dependent on the efficacy of the intervention (i.e. the potential of the intervention to prevent TB in the target group), and the degree to which target group members are identifiable and accessible for the intervention. Adherence to the intervention plays an important role if the intervention needs to be administered on a longer time scale to be effective, such as isoniazid preventive therapy, for example. The benefits of a targeted intervention may extend to the population level because onward *M.tb* transmission from the target group to the population (both target group and non-target group members) will be reduced. This *indirect effect* is dependent on the size of the direct effect and the degree to which target group members contribute to transmission in the community. The size of the overall (population-level) impact is thereby proportional to the fraction of incident TB in the population that is attributable to the target group, and that is thus (directly or indirectly) preventable.

The effects of a targeted case-finding intervention differ from those of preventive interventions. Here, target group members benefit because TB is detected at an earlier (and probably less severe) stage. An *indirect effect* in the population may accrue if the duration of infectiousness among target group members is shortened and onward transmission is thus being reduced. The overall impact of targeted case finding on TB incidence in the population is expected to be smaller compared to prevention because the incidence of TB in the target group is not directly reduced.

An example of a high-risk group that has been especially relevant for targeted TB control interventions are people living with HIV. The WHO recommends that adults and adolescents living with HIV should be screened for TB and those not considered to have active TB should be offered IPT [46]. Furthermore, early initiation of ART among HIV-infected people is expected to considerably reduce the incidence of TB [55]. In TB- and HIV-endemic populations, these interventions among people living with HIV are expected to also produce considerable population-level benefits for TB control [55-60].

Another example of a targeted intervention is the investigation of contacts of diagnosed TB cases. The WHO currently recommends that contact investigation should be conducted for household and close contacts of TB index cases who are either sputum smear-positive, have

MDR- or XDR-TB, are living with HIV or children less than 5 years of age. TB-free household contacts who are children child less than 5 years or who are living with HIV should be treated for presumed latent TB infection [61]. Household contact investigation is considered an effective way to find (and prevent) TB [62]. The extent to which within-household contact contributes to overall transmission in high-incidence populations has been debated [63]. However, mathematical modeling suggests that household contact tracing with provision of preventive therapy, could play an important role for reducing TB in high-incidence settings [64].

The WHO recommends that, while untargeted "mass screening" for TB should be avoided, systematic screening in target groups at high risk of TB should be considered for TB control in high-incidence populations [65]. Potential target groups for which screening may be considered include, for example, people with concomitant conditions such as HIV, diabetes or chronic renal failure, prisoners, immigrants and people with a history of previous TB treatment [65]. Whether systematic screening for TB in these groups may also be beneficial for TB control at the population-level is currently not known. The WHO therefore calls for more and better research to assess the impact of systematic TB screening in different populations [65].

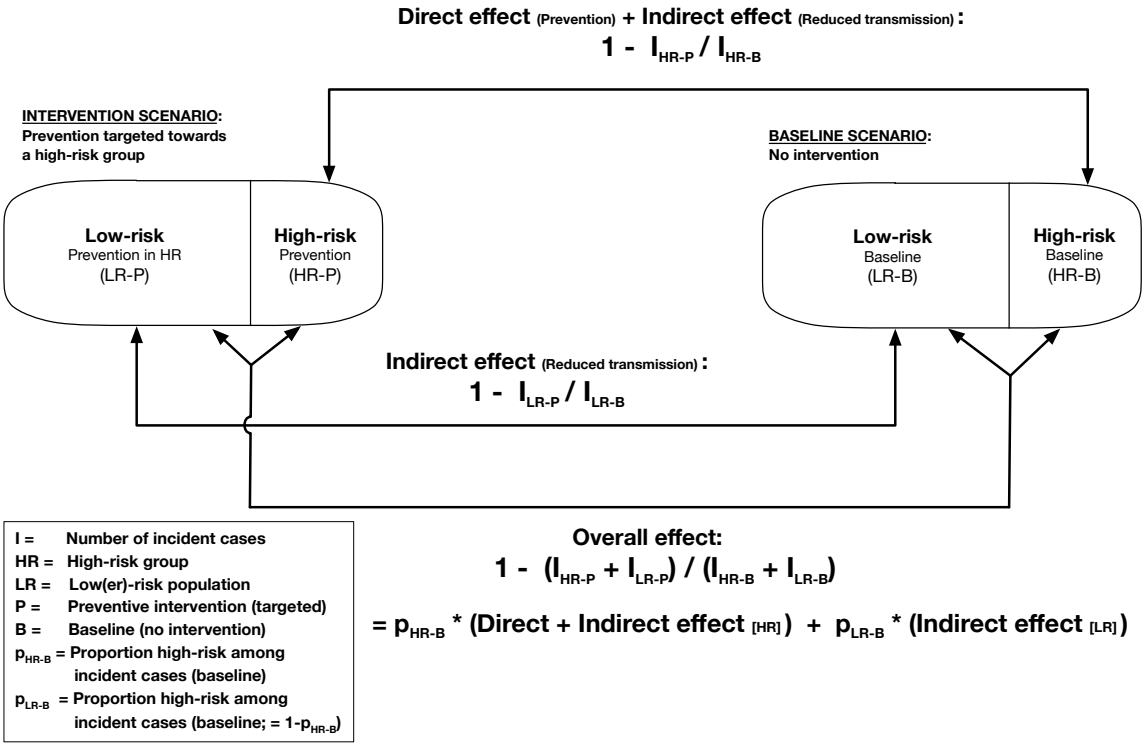

Figure 1.4. Comparison of the direct, indirect and overall effect (population-level impact) of a hypothetical preventive intervention targeted towards a high-risk group (left side) vs. a counterfactual baseline scenario (no targeted intervention; right side). The population illustrated consists of a larger fraction of low-risk individuals and a smaller fraction of high-risk individuals.

1.3. Previously treated people in the context of tuberculosis epidemics

1.3.1. General characteristics

One of the central achievements of global TB control is the roll-out of supervised and standardised TB treatment through national TB programs. In the past 10 years, 58 million people with an incident episode of TB had access to quality TB treatment under NTPs worldwide; at least 44 million incident TB cases successfully completed their treatment [5]. Every year, individuals complete TB treatment and ultimately join the generations of people who have survived the disease. The total number of people alive with a history of TB and/or TB treatment is not known. Previously treated people in the population likely constitute a heterogeneous group that is composed of individuals with previous adequate or inadequate treatment. It includes those who successfully completed their previous TB treatment, those who were previously lost to follow-up or in whom treatment had failed, and those in whom the previous treatment outcome is not known.

Previously treated people include those who have gained important knowledge and experience about TB as a disease and the treatment thereof. Many of them have been successful in sustaining lengthy treatment and recovering from TB. This experience has been used occasionally as a resource for strengthening TB control programs [66]. For example, former TB patients in Ethiopia [67], Tanzania [68] and Zimbabwe [69] have been engaged in supporting current TB patients in order to improve treatment compliance as well as in advocacy and education activities in order to raise awareness and reduce TB-related stigma in communities.

Especially in low- and middle-income countries, previously treated people constitute an especially vulnerable subgroup in the population. Catastrophic costs [70] and loss of income [71], incurred during the initial TB episode may act as a poverty trap to TB patients and their families [70-72] with consequences likely to persist after TB treatment. Pulmonary sequelae of a first episode of TB such as chronic obstructive pulmonary disease (COPD), severe bronchiectasis, residual cavitation, associated secondary bacterial and fungal infections [73], spontaneous pneumothoraxes or pulmonary hypertension may cause disability with associated further loss of income and loss in quality of life. For example, a history of previous TB treatment has been identified as an important risk factor for COPD, independent of smoking [74]. The degree of chronic lung impairment appears to increase with the number of TB episodes [75]. Other conditions and risk factors associated with the first episode of TB, such as HIV infection, diabetes, smoking and alcohol abuse may persist after TB treatment completion and further impact health and quality of life.

1.3.2. Risk of TB after successful treatment (recurrent TB)

One of the important challenges to health and well-being among previously treated people, and central to this work, is their risk of developing TB again. Recurrent TB is defined as TB that re-occurs after a person had completed a full course of TB treatment and had been considered successfully treated. Considerable rates of recurrent TB even after “optimal” TB treatment conditions have been reported. A recent meta-analysis of randomised-controlled trials of TB drugs showed that between 1.7% and 3.5% of participants who had been cured by the current standard TB regimen developed and episode of recurrent TB [76], consistent with findings of an earlier systematic review (1.7% - 2.9% recurrences after 12 months of trial follow-up) [77].

Recurrent TB is usually more common under routine TB program conditions, because treatment compliance may be reduced [78] and treatment may be less effective or inadequate if initial drug-resistance remains undetected [79]. Rates of recurrent TB after routine TB treatment vary substantially in different populations. Observational studies showed that between 1.0% and 18.9% of patients experienced an episode of recurrent TB within 12 months after successfully completing routine TB treatment in settings in China, India, South Africa and

the United States; recurrent TB was more common in high- than in low-burden settings, and among HIV-infected than among HIV-uninfected people [77].

A variety of factors associated with an elevated risk of recurrent TB have been described which include irregular and inadequate TB treatment, detected and undetected drug-resistance, extensive pulmonary disease, residual lung impairment and HIV infection [77, 80] (Table 1.1). The immunological and pathophysiological pathways under which these risk factors act towards an elevated risk of recurrent TB have not been fully understood. Of note, one study from Malawi found that having had multiple (i.e. more than one) previous TB episodes was associated with an elevated risk of recurrent TB [81].

Table 1.1. Risk factors of recurrent TB after successful treatment

Risk factor	**Description***
HIV infection	HIV infected TB patients are at 2.4 - 4.9-fold greater risk of recurrent TB compared to uninfected individuals [77, 81-83] have been estimated in studies among miners in South Africa. Lower CD4 cell count is associated with higher risk of recurrent TB [84]. A randomised-controlled trial showed that extending treatment among HIV-infected TB patients from 6 to 12 months reduced the risk of recurrent TB [85].
Intermittent and irregular TB treatment	Cured TB patients who were on intermittent (thrice weekly) compared to daily treatment are at 2.2-times greater risk of recurrent TB according to a recent meta-regression analysis of RCTs [76]. Also, patients who completed standard TB treatment but had taken their medication irregularly appear to be at 2.5-fold greater risk of TB recurrence compared to those who took their medication regularly [78].
Drug-resistant TB	Patients with drug-resistant TB [78, 83] are at 2.7-4.8-times greater risk of recurrent TB. High rates recurrent TB have been reported among patients successfully treated for multidrug-resistant (MDR-) TB [86].
Extensive disease and pulmonary cavitation	The pre-treatment (radiographic) extent of lung tissue involved in TB [87, 88], pre-treatment cavitation (3.0-fold greater risk [88]) and pre-treatment sputum smear grading [89] have been shown to be associated with TB recurrence. Also, a greater risk among patients with post-treatment (residual) cavitation (4.1-fold [82]), and post-treatment TB scarring (trend: 1.6-fold increase for one or two, 4.0-fold increase for three or more lung zones involved [83]) have been observed as independent risk factors of TB recurrence.
Delayed sputum conversion (and undetected non-conversion)	Persistent *M.tb* culture-positive TB at month 2 of TB treatment has been reported to be independently associated with recurrent TB (2.8-fold greater risk) [88, 90], while others have not found this association [77]. Recurrent TB is usually defined according to best evidence that the previous treatment outcome was successful. Patients with positive *M.tb* culture at a later time/towards the end of treatment are therefore not normally included in the measure of recurrent TB. However, under programmatic conditions, patients often complete their treatment without bacteriological confirmation of cure. Using the above definition for recurrent TB, it is expected that individuals with late (undetected) culture-positive TB who were considered successfully treated are at high risk of subsequent TB [91]
Other risk factors	More than one previous episode of TB (2.3-fold greater risk [81]), chronic lung disease (5.3-fold [92]), silicosis [93], smoking (3.1-fold [78]), alcoholism (2.3-fold [78]), and being underweight at TB diagnosis (2.8-fold) were reported to be independently associated with TB recurrence.

* The table shows best estimates of the effect of each risk factor estimated in various studies cited. For simplification, different effect measures such as risk-, rate- and odds ratios are states as “risk” in this table.

1.3.3. Mechanisms of TB recurrence: endogenous reactivation and exogenous reinfection

A spectrum of microbiological and clinical outcomes is possible under TB drug treatment. This spectrum reaches from sterilising cure (i.e. the complete killing of endogenous *M.tb* with clinical recovery), to non-sterilising cure (i.e. clinical recovery with survival of non-replicating "quiescent" *M.tb*), to treatment failure (i.e. the persistence of replicating bacteria with no or incomplete clinical recovery) [94]. While failure of TB treatment is verifiable through persistent culture- (and/or smear-microscopy-) positive sputum results during treatment, the probabilities of sterilising- and non-sterilising cure are usually not known. However, recent findings of *M.tb* mRNA and of persistent pulmonary lesions* after curative treatment suggest that non-sterilising cure may be a common outcome, and point towards a role for host-immunity for maintaining cure after TB treatment [95]. Recurrence of TB may thus be the result of endogenous reactivation, also termed 'relapse', if *M.tb* had persisted due to non-sterilising treatment and immunity had subsequently failed to maintain a disease-free state. Alternatively, TB after curative treatment may recur independently of reactivation, due to an exogenous reinfection event [96]. While relapse is expected to occur early (i.e. within months) after the completion of TB treatment [97-99], reinfection TB is expected to occur later, because the time between treatment completion and disease recurrence also involves the time to becoming re-exposed and reinfected.

Questions about the relative contribution of endogenous reactivation vs. exogenous reinfection to recurrent TB after curative treatment have been the subject of considerable scientific debate for many years [80, 100]. Historically, reinfection had been emphasised [101, 102] and doubted [103] to be a possible cause of recurrent TB. The advent of molecular techniques to characterise and distinguish *M.tb* strains via their DNA patterns such as spoligotyping, MIRU-VNTR†, *IS6110*-based Restriction Fragment Length Polymorphism (RFLP), and more recently Whole-Genome Sequencing (WGS) of *M.tb* has created novel opportunities to study the underlying mechanisms of disease recurrence. In the 1990s, exogenous reinfection was confirmed as a possible [104] and potentially important [96, 105] underlying cause of recurrent TB. In subsequent studies, proportions of recurrent TB that were due to exogenous reinfection varied considerably, i.e. between 0% and 100%, potentially due to differences in follow-up time after curative treatment [80]. High rates of recurrence due to reinfection had been confirmed especially among people living with HIV (see below) [82]. Mathematical models suggest that the proportion of recurrences that is due to reinfection in populations is proportional to the background rate of TB [106, 107].

1.3.4. Recurrent TB: evidence from a high-incidence setting in Cape Town

In the past two decades, high rates of recurrent TB have been reported from several TB high-incidence settings. One of these settings is located in suburban Cape Town and consists of two adjacent communities with a local population of approximately 39,000 people, and with an area of 3.4 km^2 [108]. Two local primary health-care clinics provide routine TB diagnosis and treatment since 1996 in this setting. Local TB case notification rates have since continuously exceeded 1,000 per 100,000 people per year. Persistently high annual risks of infection (3.7% in 1999 and 4.1% in 2005 [109]) suggested that conventional TB control, while improving individual outcomes, did not reduce transmission in these communities [110].

In 1999, a local study using DNA fingerprinting provided one of the first definitive records of recurrent TB due to exogenous reinfection in a high-incidence setting [105]. Van Rie et al. [96] reported from this study that reinfection was the underlying cause of TB recurrence after curative treatment in 12 (75%) of 16 patients. Consistent with this study, Verver et al. [111] reported in 2004 that TB recurrence had been due to reinfection in 24 (77%) of 31 enrolled patients who had been previously cured from TB in the communities. They estimated an annual rate of recurrent TB due to reinfection of 2%, exceeding 4-times the age-adjusted incidence of new TB in this setting [111]. Den Boon et al. [112] suggested in 2005 that previously treated

* identified via positron emission tomography–computed tomography (PET-CT)

† MIRU: mycobacterial interspersed repetitive units; VNTR: variable number of tandem repeats

people may contribute considerably to the prevalent TB burden in the two communities. They found that of 26 prevalent culture-positive TB cases detected during a household-based lung health survey in the communities, 10 (38%) had been previously treated for TB in the communities. These 10 adults together had a history of 15 previous TB treatment episodes in total, of which 8 had resulted in cure, 3 in loss-to follow-up and 1 in treatment failure (3 unknown) [112].

1.3.5. Recurrent TB: evidence from other high-incidence settings in Africa

Variably high rates of recurrent TB among both HIV-infected and -uninfected people have been reported from several other high-incidence settings in Southern Africa, including from Kenya [113], Malawi [114, 115], Tanzania [116], South Africa [81-83, 117], Uganda [118], and Zambia [119]. Higher rates are consistently observed among people infected with HIV than among uninfected people (Figure 1.5). ART was found to partially reduce the rate of recurrent TB [115]. There is inconclusive evidence about the extent to which exogenous reinfection contributes to TB recurrence. Studies in a population of gold miners in South Africa suggested that the high risk of recurrent TB among people living with HIV is due to an increased risk of exogenous reinfection, whereas recurrence among HIV-uninfected people is mostly due to endogenous reactivation (relapse) [82, 114]. However, others [81, 111] have emphasised that reinfection may be equally important as a mechanism of recurrence in HIV uninfected people. Glynn et al. [81] reported that the rates of recurrent TB in both HIV-uninfected and HIV-infected people were several-fold (10-fold vs. 5-fold, respectively) higher than the corresponding rates of incident new TB in the population and suggested that heterogeneity in individual susceptibility may explain the observed high rates of reinfection TB relative to new TB.

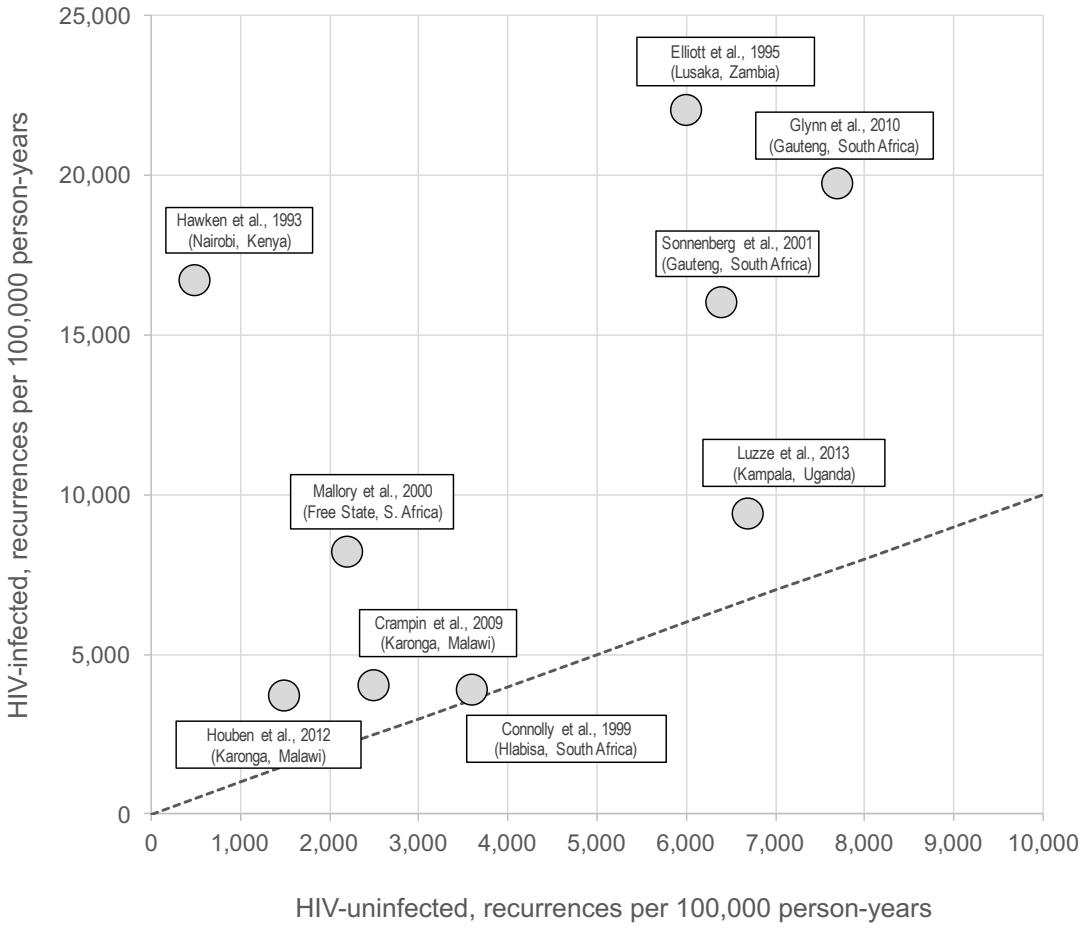

Figure 1.5. Overview of studies conducted in Southern Africa that have estimated rates of recurrent TB stratified by HIV status, 1993-2013; the dashed line shows equal rates for orientation

1.3.6. Risk of TB after unfavourable treatment outcome

People with a history of previous TB treatment may also include those in whom previous treatment failed, and those who were lost to follow-up before completing their treatment. TB patients in whom treatment failed, for example due to extensively drug-resistant TB, might be considered incurable and discharged to the community where they may survive for a variable period of time and remain infectious, posing a risk of transmission to others [27]. Studies of the risk of TB after previous loss to follow-up from treatment are rare, but have reported high rates of disease reactivation [111] and high probabilities of either bacteriologically-positive TB or death [120] after incomplete TB treatment.

1.3.7. Targeting TB control toward previously treated people

Individuals with a history of previous TB treatment had been in the focus of historical TB control programs and activities several decades ago. Former TB patients had remained under public health supervision in many parts of the world, including in North America, Europe and in the countries of the former Soviet Union. Lifelong supervision after TB treatment continues to form an integral part of TB control in Russia and other former Soviet Union countries nowadays, where previously treated people are allocated to “dispensary groups” and regularly undergo radiological screenings for TB [121-123]. In Western Europe and North America, the practice of lifelong follow-up examinations had been debated in the early 1970s [124-129], and was later abandoned [130], mainly because TB treatment had significantly improved [131, 132] and follow-up of adequately treated TB patients was deemed to be costly and inefficient [130].

In the past two decades, TB control programs in high-incidence settings have prioritised resources to detect new TB cases and to ensure adequate and supervised TB treatment in order to achieve high cure rates. However, reports about high rates of TB recurrence after curative treatment, challenges in the management of previously treated TB patients [133] and the threat of emerging drug-resistant disease have raised awareness about TB among former patients [7, 134]. The need for targeted interventions to reduce the burden of recurrent TB in TB- and HIV-endemic settings had been emphasised more than a decade ago [135], but little effort has since been invested to evaluate suitable strategies.

Options for targeted interventions among previously treated people can be divided into three main categories.

(1) *Interventions at the time of the initial TB treatment episode* include the provision of intensified and extended TB treatment [136] among selected high-risk patients. Extending the duration of a first treatment episode was shown to reduce the risk of recurrent TB among HIV-infected individuals in a large randomised-controlled trial in the Democratic Republic of Congo (formerly known as Zaire) [85, 136]. Furthermore, the potential effect of an adjunct vaccine or immunotherapy for preventing recurrent disease has been emphasised [137] but data are not yet available.

(2) *Interventions after TB treatment to prevent recurrent TB* include the provision of secondary preventive therapy and post-treatment vaccination. A strong protective effect of IPT on recurrent TB has been documented [138-140]. However, prospective data from randomised-controlled trials remains sparse, restricted to people living with HIV, and do not take ART or drug-resistance into account [140]. A recent phase-2a trial of post-treatment vaccination has recently been completed in South Africa [141]; data are not available yet.

(3) *Interventions of targeted case finding and follow-up examinations among former TB patients* may help shorten the time to detecting recurrent TB. The WHO counts individuals previously treated for TB as one of the potential target groups for systematic TB screening (Guideline 2013). Data on the impact of these targeted case-finding strategies are not available to date.

1.4. Mathematical models of tuberculosis control

1.4.1. Overview

Mathematical models have provided novel insights into the natural history of infectious diseases, their distributions, transmission dynamics and underlying determinants in populations as well as the impact and cost implications of control interventions. Over the past two decades, models have been increasingly used to evaluate the impact of existing TB control measures as well as to guide the development and implementation of novel interventions. Models most commonly used in studies of TB control include population-based, transmission-dynamic models that simulate temporal trends of TB epidemics in populations and decision-tree (operational) models that compare alternative decision processes, for example the use of different diagnostic algorithms, in terms of their public health benefits and cost-effectiveness.

Population-based models have been used to project the impact and cost-effectiveness of various TB control measures, including preventive interventions (such as vaccination [142-144] or preventive therapy [47, 145]), TB case detection (case finding) [15, 146-148], novel TB diagnostics and better diagnostic algorithms [149-151], and optimising TB treatment [15]. Mathematical models have further addressed the benefits that accrue for TB control if concomitant diseases and conditions are more effectively controlled. For example, studies have used modeling to project the TB control impact of scaling up HIV testing and ART [60, 152] and of improving diabetes control [153]. Mathematical models have also been used to evaluate specific interventions for controlling the burden of drug-resistant TB [154-156].

A well-known example of a mathematical modeling study that has guided global TB control efforts had been conducted by Dye et al. and published in 1998 [15]. In this study, Dye et al. developed a compartmental model to project the prospects for worldwide TB control under the DOTS strategy in high- and low-HIV prevalence countries (Figure 1.6). The model suggested that scaling up TB case detection rates to 70% and achieving cure rates of 85% would lead to considerable reductions in TB incidence and mortality [15]. Both achieving 70% case detection and 85% treatment success annually had been endorsed by the WHO and the Stop TB Partnership as global targets for TB control during the early phase of the global TB control strategy (see 1.2) [8].

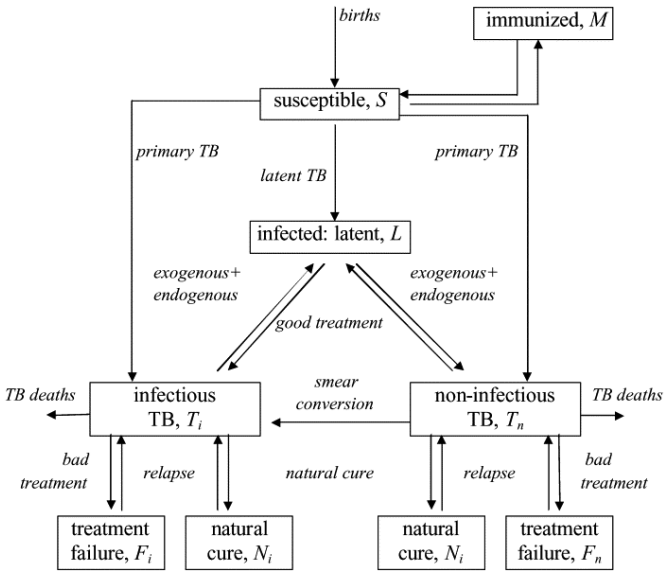

Figure 1.6 Flow-diagram of a transmission-dynamic compartmental model that was used by Dye et al. (1998) to estimate the impact of the WHO-approved global TB control strategy "Directly observed treatment, short course" in low and high HIV prevalence settings. The model distinguishes between core states of TB: susceptible [S] and immunised [M], latently infected [L], infectious [Ti], non-infectious [Tn] and cured [Ni] individuals, and those in whom treatment failed [Fi and FN]. Upon "good treatment", infectious [Ti] and non-infectious [Tn] TB cases transition back into the latently infected [L] compartment (Figure source: [15]).

1.4.2. Previously treated people in models of TB control

Population-based models of TB control usually account for the subgroup of people who had recovered from TB through treatment and the subsequent risk of TB and make a number of simplifying assumptions about the natural history of TB among previously treated people.

Several models have assumed that people remain latently infected after completing TB treatment, and that their rate of reactivation, reinfection and disease progression (upon reinfection) is identical to latently infected people without previous TB treatment [7, 72]. These studies usually employed model structures that would allow circular transitions, in which people who completed TB treatment transit back into the latently infected compartment (compare Figure 1.6). Other models included additional compartments for recovered people to allow for differential rates of TB reactivation but either assumed no reinfection at all, or that rates of re-exposure, reinfection and disease progression were independent of TB treatment history [65, 81-83]. Furthermore, models usually assumed that treatment-experienced cases of infectious TB do not differ from treatment-naïve cases in terms of their infectiousness, their disease duration and time to detection. Finally, models assumed that TB treatment-experienced people do not differ from treatment-naïve people in terms of their probability to successfully complete TB treatment, or to fail treatment, or to die from TB.

Previously treated people have been considered in mathematical models of TB. However, to date, no modeling study has addressed the potential impact of targeting TB control interventions toward this high-risk group as a strategy to strengthen TB control.

1.5. Knowledge gaps

TB after loss to follow-up from treatment

To date, studies have aimed to investigate the rate of recurrent TB among successfully treated individuals, but few studies have been able to quantify the rate of TB among people who were previously lost to follow-up from treatment. Only one previous study from suburban Cape Town which focussed primarily on reinfection TB after successful treatment had also reported that 47 (28%) of 165 patients previously lost to follow-up had been re-treated for bacteriologically-confirmed TB, suggesting a high risk of TB reactivation after incomplete treatment. A study from Northern Vietnam had found that of 42 patients lost to follow-up or transferred out before the end of treatment, 38 had died, and only one of 24 available for follow-up was found to be *M.tb* culture-positive (untreated) [120]. The risk of TB after loss to follow-up from routine TB treatment in relation to successful treatment and in the context of other potential risk factors are currently not well understood. Furthermore, in the context of high rates of recurrent TB after successful treatment, little is known about the extent to which loss to follow-up (incomplete treatment) contributes to the TB burden among previously treated people. Better knowledge about the role of loss to follow-up for the rate and burden of infectious TB may help to estimate whether improving treatment adherence may be sufficient to prevent TB among previously treated people, or whether interventions among those after successful treatment may be more promising.

Relapse vs. reinfection TB in high-incidence settings

Several studies of recurrent TB after successful treatment have been conducted in high-incidence settings. However, relatively few had employed molecular techniques of strain-type DNA patterns to investigate endogenous reactivation (relapse) vs. exogenous reinfection as underlying mechanisms of recurrence. Before the research described in this dissertation was conducted, the largest study of relapse and reinfection had been based on 65 recurrent TB patients from an occupational (gold mining) setting in South Africa [82]. Other molecular epidemiological studies had been of smaller size, varied in terms of follow-up time and yielded inconclusive results about the contribution of exogenous reinfection to recurrent TB (0 - 100%) [80]. Very few studies had estimated relapse and reinfection over time. Large longitudinal

studies of were therefore needed to better understand the contribution of exogenous reinfection to recurrent TB in settings with a high prevalence of TB [80, 100].

Recurrent TB at the population level and the impact of targeted interventions

High rates of TB recurrence had been reported from several TB- and HIV-endemic communities in Southern Africa, and the need for targeted interventions to prevent recurrent TB has been emphasised more than a decade ago [136]. Whether recurrent TB may also significantly contribute to the overall TB burden and associated *M.tb* transmission in TB high-incidence populations has not been investigated. Better knowledge about recurrent TB at the population level would help to estimate whether the benefits of these targeted interventions could also extent to the population level.

Although mathematical models have projected the impact of improving TB treatment outcomes as a means of reducing relapse and associated transmission [15], to date, none have considered the impact of preventive and case-finding interventions after completion of TB treatment. Given the high rates of recurrent TB observed in several high-incidence settings and preliminary findings of a high prevalence of (undetected) TB among former TB patients in suburban Cape Town [112], we felt that a mathematical model to project the impact of these targeted interventions in a high-incidence setting was useful.

1.6. Aim and overview of studies

The aim of the research presented in this dissertation was to characterise the risk of TB among people with a history of previous TB treatment and to project the impact of control interventions targeted at this subgroup on the trajectory of TB epidemics in high-incidence settings.

Towards this aim, I used routine TB program data to investigate, in a specific high-incidence setting in suburban Cape Town, the rate of re-treatment for smear-positive TB dependent on whether individuals had completed their previous TB treatment (Chapter 2). I used routine TB programme data and paired strain-type DNA fingerprinting results from diagnostic samples to investigate the distinct temporal dynamics of endogenous reactivation (relapse) and exogenous reinfection TB over the time that had passed since the successful completion of treatment (Chapter 3). The central question, whether interventions targeted to previously treated people might impact the trajectory of the TB epidemic, is then directly addressed through mathematical modeling (Chapter 4). I used a calibrated transmission-dynamic mathematical model to project the impact of two specific control interventions, (1) targeted active TB case finding (TACF) among individuals who had previously completed TB treatment and (2) TACF combined with secondary isoniazid preventive (2°IPT) therapy, on the trajectory of TB in this high-incidence setting. I conducted two further studies to determine whether projections from our mathematical model may be relevant to other high-incidence settings in Southern Africa. Specifically, I investigated the extent to which previously treated people contribute to the prevalent TB burden in 24 communities in South Africa and Zambia (Chapter 5), and to the (detected) incident TB burden in the 52 South African health districts (Chapter 6). I finally discuss the evidence in the context of the literature, strengths and limitations of this work, the relevance to TB control in high-incidence settings, and recommendations for future research (Chapter 7).

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Chapter 2: The rate of sputum smear-positive tuberculosis after treatment default in a high-burden setting: a retrospective cohort study

Overview:

This chapter consists of a published article and reports findings from a retrospective cohort study conducted on the basis of 1996-2008 TB treatment register data from a high-incidence in suburban Cape Town. The aim of this study was to investigate the rate of re-treatment for sputum smear-positive TB among previously treated people who were lost to follow-up from treatment (formerly termed "treatment default")[*] vs. those who had completed their treatment. We further aimed to investigate whether treatment duration and sputum conversion prior to loss to follow-up were associated with re-treatment for smear-positive TB.

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My contribution:

I conceived and designed the study with input from N Beyers and DA Enarson. I collaborated with R Dunbar and the data management team in data cleaning, consistency checking and validation of the routine TB program data used, and record linkage of individual treatment episodes. I planned and conducted the data analysis, wrote the first manuscript draft, finalized and submitted the manuscript. R Dunbar led the data management and record linkage for this study. All authors contributed to the design of the study, interpretation of the results, and writing/revision of the manuscript draft.

[*] By the time this article was published, treatment default was an official term in standard TB recording and reporting. It was assigned as the treatment outcome to TB patients who did not start treatment or whose treatment was interrupted for two consecutive months or more. In the 2013 revision of the definitions and reporting framework for tuberculosis, the World Health Organization replaced the term "treatment default" with "loss to follow-up from treatment" in order to avoid judgmental (and potentially stigmatising) language. While the term "treatment default" is avoided in other parts of this dissertation, for copyright reasons, it is left unchanged in this chapter (and on one occasion in the following chapter) as in the original print publication.

The rate of sputum smear-positive tuberculosis after treatment default in a high-burden setting: a retrospective cohort study

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Rationale: High rates of recurrent tuberculosis after successful treatment have been reported from different high burden settings in Sub-Saharan Africa. However, little is known about the rate of smear-positive tuberculosis after treatment default. In particular, it is not known whether or not treatment defaulters continue to be or become again smear-positive and thus pose a potential for transmission of infection to others.

Objective: To investigate, in a high tuberculosis burden setting, the rate of re-treatment for smear-positive tuberculosis among cases defaulting from standardized treatment compared to successfully treated cases.

Methods: Retrospective cohort study among smear-positive tuberculosis cases treated between 1996 and 2008 in two urban communities in Cape Town, South Africa. Episodes of re-treatment for smear-positive tuberculosis were ascertained via probabilistic record linkage. Survival analysis and Poisson regression were used to compare the rate of smear-positive tuberculosis after treatment default to that after successful treatment.

Results: A total of 2,136 smear-positive tuberculosis cases were included in the study. After treatment default, the rate of re-treatment for smear-positive tuberculosis was 6.86 (95% confidence interval [CI]: 5.59–8.41) per 100 person-years compared to 2.09 (95% CI: 1.81–2.41) after cure (adjusted Hazard Ratio [aHR]: 3.97; 95% CI: 3.00–5.26). Among defaulters, the rate was inversely associated with treatment duration and sputum conversion prior to defaulting. Smear grade at start of the index treatment episode (Smear3+: aHR 1.61; 95%CI 1.11–2.33) was independently associated with smear-positive tuberculosis re-treatment, regardless of treatment outcome.

Conclusions: In this high-burden setting, there is a high rate of subsequent smear-positive tuberculosis after treatment default. Treatment defaulters are therefore likely to contribute to the pool of infectious source cases in the community. Our findings underscore the importance of preventing treatment default, as a means of successful tuberculosis control in high-burden settings.

Introduction

A major principle in tuberculosis control is the necessity to ensure that patients adhere to a full course of treatment. At least six months anti-tuberculosis multidrug chemotherapy is required to achieve cure in smear-positive tuberculosis patients with initially drug-susceptible disease [1]. Shorter treatment regimens result in high rates of disease recurrence within 24 months after treatment [2–4].

Adherence to a full course of treatment is therefore expected not only to prevent disease recurrence, but also to contribute to a reduction in tuberculosis burden at population level [5]. The latter is based on the assumption that patients not successfully treated remain contagious or experience recurrent disease and contribute to an increased burden of disease and transmission of tuberculosis within the community.

Non-adherence to a full course of anti-tuberculosis treatment is usually termed 'treatment default', defined as interruption of treatment for at least two consecutive months. Risk factors for treatment default such as lack of knowledge and family support, distance between home and health care facility, and drug side effects have been widely studied [6–8], but little is known about the fate of patients after defaulting from anti-tuberculosis treatment. It is not known whether or not treatment defaulters continue or return again sputum smear-positive and thus pose a potential for transmission of infection to others.

While treatment defaulters could be specifically targeted by interventions to prevent default, to retrieve those who have defaulted and to prevent subsequent recurrence of disease [9], such interventions require scarce resources that must be rationed properly based on an assessment of the size of the problem and the ease of its solution.

This study was conducted in a setting with a high tuberculosis burden in South Africa. High rates of recurrent tuberculosis after successful treatment have been reported from this and other settings in Sub-Saharan Africa. Exogenous re-infection rather than relapse seems to be the major underlying cause of recurrence in successfully treated cases [10–12], with the proportion of re-infection increasing with background tuberculosis incidence [13], and with human immunodeficiency virus (HIV) co-infection being an important risk factor [14–16].

In the context of frequent tuberculosis re-infection, little is known about the significance of treatment default as a risk factor for smear-positive tuberculosis.

The objective of this study was to investigate the rate of re-treatment for smear-positive tuberculosis, after defaulting from an initial treatment episode. We hypothesised that in a setting with a high tuberculosis burden, sputum smear-positive tuberculosis cases who default from treatment are more likely to return for treatment with smear-positive disease compared to those who successfully complete their treatment. We further aimed to investigate whether treatment duration and sputum conversion prior to default are associated with re-treatment for smear-positive tuberculosis.

Methods

Study Setting

Two adjacent urban communities covering an area of 3.4 km^2 with 36,000 inhabitants of low socio-economic status and a high-burden of tuberculosis in metropolitan Cape Town, South Africa [17]. The DOTS strategy [18] was introduced in 1996 to both communities where two primary health-care clinics provide treatment and routinely record and report cases started on treatment. Treatment regimens were in accordance with standards for South Africa [19]: For cases never previously treated (new cases), this was six months of daily isoniazid and rifampicin supplemented by daily pyrazinamide and ethambutol for the first two months, extended for a further month if the sputum smear was positive at the end of two months. Treatment for re-treatment cases consisted of daily isoniazid, rifampicin and ethambutol for eight months supplemented with daily pyrazinamide and streptomycin in the first three months.

Treatment outcomes were documented by local health care staff according to standard definitions [19]. This included cure, for patients who were smear-positive at initiation of treatment and smear-negative at, or one month prior, to the completion of treatment and also on at least one previous occasion, and treatment completed, for patients who had completed treatment but without proof of cure due to smear results not available on at least two occasions prior to the completion of treatment. The term 'treatment success' includes both, cure and treatment completed. The outcome of treatment default was recorded for a tuberculosis case whose treatment was interrupted for more than two consecutive months before the end of the treatment period. Health care staff members were advised to record the date of treatment

default as the last date at which the patient picked up medication before defaulting, and, in the case of interruption for less than two months, to trace the patient and to prolong treatment in order to compensate for missed doses.

Data Sources

Routine program data entered by local health care staff from both clinics into paper-based tuberculosis treatment registers for the years 1996 to 2008 were captured in an electronic database. Missing values for treatment end date and treatment outcome were ascertained as follows: If no end date (default date) was documented in the treatment register, the patient file was reviewed and the last day at which the patient was documented to have taken up medication was accepted as the end date. If no treatment outcome was documented in the register, patient files were reviewed and the documented treatment outcome was updated in the database.

Study Design

A retrospective cohort study was conducted, comparing sputum smear-positive tuberculosis cases who successfully completed treatment to those who defaulted from treatment between 1996 and 2008. From the database, we selected all episodes of treatment with a documented smear-positive sputum result at start of treatment and a treatment outcome of either cure, treatment completed or treatment default. 'Sputum smear-positive' was defined by at least one sputum sample documented smear-positive for acid-fast bacilli by fluorescence microscopy. Episodes of second-line treatment, episodes of treatment for smear-negative tuberculosis, episodes with treatment outcomes other than success or default and those without a treatment outcome documented, were not included in the study. We further excluded episodes with a treatment end date after 31st October 2008, in order to allow for sufficient time to re-treatment (see below).

All treatment episodes included in the study were defined as index episodes. An episode of re-treatment for smear-positive tuberculosis (study outcome) was defined as any subsequent episode of treatment for documented smear-positive tuberculosis recorded for the same individual person, with a minimum time of two months between the end date of the index episode and the record date of the re-treatment episode.

Ascertainment of Smear-positive Tuberculosis Re-treatment

We used Registry Plus™/Link-Plus [20] probabilistic record linkage software to identify episodes of re-treatment for smear-positive tuberculosis recorded in the treatment registers. The software matches records on the basis of matching variables and assigns a probability score for a true (individual) match of two independent records. Each index treatment episode included in the study was screened for matches with any subsequent treatment episode recorded for the same individual person in the treatment registers. First and family name (case-sensitive), sex and year of birth were chosen as matching variables.

Matches of treatment episodes identified from the record linkage were initially reviewed and classified on the basis of concordance of the matching variables into perfect matches, highly probable matches and probable matches: A 'perfect match' was defined by 100% concordance of each, first and surname, sex and year of birth. 'Highly probable matches' had minor spelling differences in first- or surname and 100% concordance of both, sex and year of birth. 'Probable matches' had 100% concordance or minor spelling differences of first- and surname and 100% concordance of either sex or year of birth but discordance or original paper-based treatment registers and, if necessary, patient folders as a reference. In line with the study definition for episodes of re-treatment for smear-positive tuberculosis, matches were excluded if the time period between the end date of the index episode and the record date of the re-treatment episode was shorter than two months.

Data Analysis

STATA™ 10.1 statistical application (Stata Corp, College Station, TX, USA) was used for data analysis. Survival analysis and Poisson regression were used to determine rates of re-treatment for smear-positive tuberculosis after treatment default vs. after cure/completion. Cases entered the study on the date when they successfully completed or defaulted from the index treatment episode and were censored on the date when the first re-treatment episode (smear-positive) was recorded in the registers or else at the end of the study period. A multivariable regression model was developed using a step-wise forward technique: co-factors documented at the index episode were considered if they reached $P<0.10$ significance at univariable regression and resulted in a change of +/- 0.1 Rate Ratio for the principal determinant under study. Among treatment defaulters, sub-group analysis was conducted, taking into consideration treatment duration, and sputum conversion prior to defaulting, as documented at the end of the intensive phase of treatment (month 2–3).

Ethics Statement

Permission to access the program data for research has been granted by the City of Cape Town (research ID = 10142), the custodian of the data. The study was approved by the Committee for Human Research, Faculty of Health Sciences, Stellenbosch University (N09/05/144 and amendments 1 and 3) and also by the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease. This was a retrospective analysis of routine data and therefore we requested and were granted a waiver of individual informed consent from the ethics committee. The use of a unique subject ID ensured anonymous analysis. Only the senior data staff had access to personal identifiers which were removed after the record linkage process.

Results

A total of 2,521 tuberculosis cases with an episode of first-line treatment for smear-positive tuberculosis were recorded in the treatment registers 1996–2008. Of these, 2,136 were included in the study, 1,743 with documented cure, 126 with treatment completion and 267 with treatment default. A breakdown of cases included and excluded is shown in Figure 1.

Of all cases included, 1,274 (59.6%) were male, median age was 34 years, and 1,065 (49.9%) had an HIV test result documented, 110 (10.3%) of whom were HIV positive.

Re-treatment for Smear-positive Tuberculosis

For 291 (13.6%) of the 2,136 smear-positive cases included in the study, an episode of re-treatment for smear-positive tuberculosis was identified via record linkage and confirmed via manual review. A detailed overview of the record linkage and manual review is shown in Figure 2.

Median time between the end date of the index episode and the record date of the subsequent episode was 17 months. Ninety-two of the 291 cases with re-treatment for smear-positive tuberculosis (31.6%) had defaulted at the index treatment episode.

The rate of re-treatment for smear-positive tuberculosis was 2.09 (95% confidence interval [CI]: 1.81–2.41) per 100 person-years after cure, 2.19 (95%CI: 1.29–3.69) after treatment completion, and 6.86 (95%CI: 5.59–8.41) after previous treatment default.

For tuberculosis cases defaulting during the index episode, the unadjusted Hazard Ratio (HR) of re-treatment was 3.29 (95%CI: 2.56–4.22) using cases with cure as the baseline (Table 1). Sputum smear grading at start of the index treatment episode (Smear 3+: HR 1.61; 95%CI: 1.11–2.33) and age (>40 years: HR 0.40; 95%CI: 0.25–0.65) were each independently associated with smear-positive tuberculosis re-treatment (Table 2). After adjusting for initial smear grade and age, the HR for smear-positive tuberculosis re-treatment among defaulters was 3.97 (95%CI: 3.00–5.26).

In cases after treatment default, there was a steep increase in the cumulative rate of smear-positive tuberculosis within the first two years. By the end of the second year, 27.9% (95% CI 22.8% – 33.8%) had experienced a re-treatment episode, compared to 5.8% (95%CI: 4.7%–7.0%) of cases after cure. The failure function for cases after default differed according to smear-grading at start of treatment (P = 0.04; after treatment success: P = 0.05) (Figure 3).

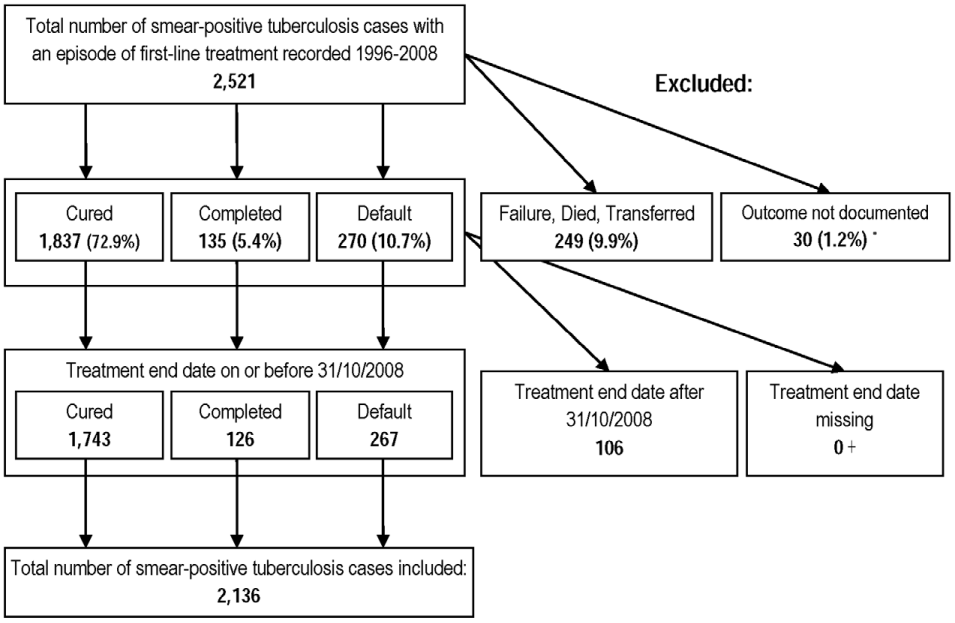

Figure 1. Overview of smear-positive tuberculosis cases included in and excluded from the study. doi:10.1371/journal.pone.0045724.g001

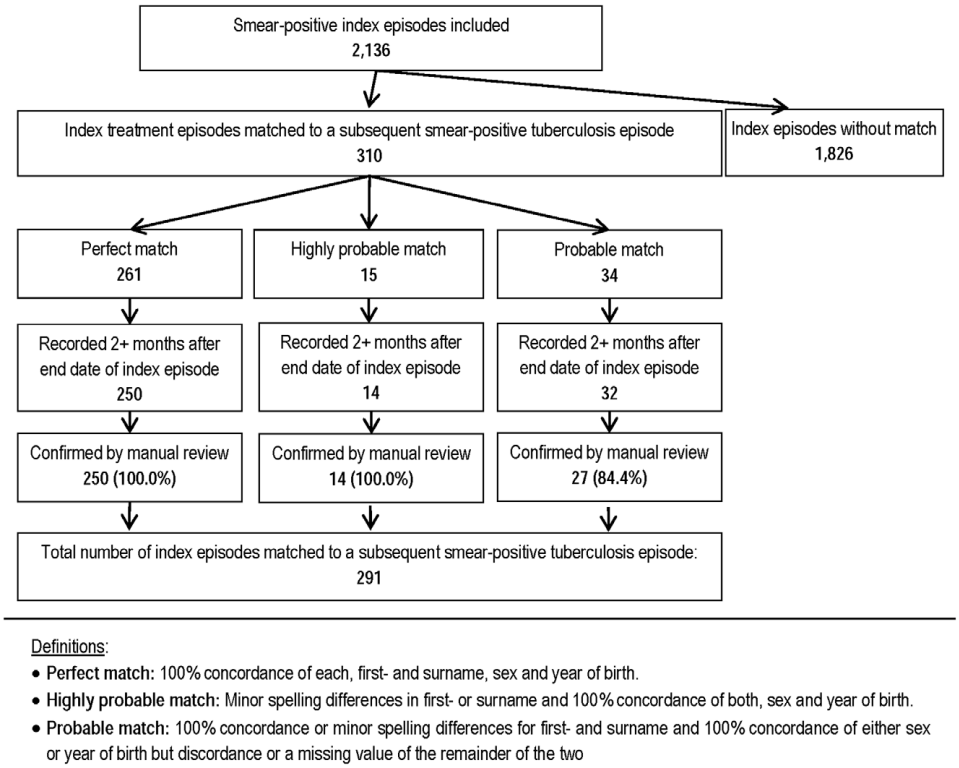

Figure 2. Ascertainment of subsequent episodes of re-treatment via record linkage and manual review for the study. doi:10.1371/journal.pone.0045724.g002

Table 1. Univariable analysis of index episode risk factors for subsequent smear-positive tuberculosis re-treatment (N = 2,136).

	Total re-treatment cases	PY	Rate (per 100 PY)	Crude hazard-ratio (95% CI)	P-value
Overall	291	10844	2.68 (2.39–3.01)		
Treatment outcome					<0.001
Cured	185	8863	2.09 (1.81–2.41)	1	
Completed	14	640	2.19 (1.29–3.69)	1.05 (0.61–1.80)	
Defaulted	92	1341	6.86 (5.59–8.41)	3.29 (2.56–4.22)	
Sex					0.005
Female	93	4352	2.14 (1.74–2.62)	1	
Male	198	6492	3.05 (2.65–3.51)	1.43 (1.12–1.83)	
Age					0.002
0–18	30	758	3.96 (2.77–5.66)	1	
19–39	193	6646	2.90 (2.52–3.34)	0.73 (0.50–1.08)	
40+	68	3430	1.98 (1.56–2.51)	0.50 (0.33–0.77)	
Patient category					0.03
New	181	7384	2.45 (2.12–2.84)	1	
Re-treatment	110	3424	3.21 (2.67–3.87)	1.31 (1.03–1.66)	
HIV status					0.10
negative	111	3542	3.13 (2.60–3.77)	1	
positive	12	383	3.13 (1.78–5.52)	1.00 (0.55–1.81)	
unknown	168	6919	2.43 (2.09–2.82)	0.77 (0.61–0.98)	
Smear grade*					0.03†
Smear 1+	35	1588	2.20 (1.58–3.07)	1	
Smear 2+	48	1576	3.05 (2.30–4.04)	1.38 (0.89–2.14)	
Smear 3+	154	4641	3.32 (2.83–3.89)	1.51 (1.04–2.17)	
Smear conversion (month 2)					0.03
Yes (smear-negative)	189	8297	2.28 (1.98–2.63)	1	
No (smear-positive)	60	1899	3.16 (2.45–4.07)	1.39 (1.04–1.85)	
Treatment duration					<0.001
>8 months	53	1858	2.85 (2.18–11.32)	1.47 (1.06–2.03)	
6–8 months	120	6177	1.94 (1.62–2.32)	1	
4 – <6 months	88	2431	3.62 (2.94. –4.46)	1.86 (1.42–2.45)	
<4 months	30	379	7.92 (5.54–12.23)	4.08 (2.73–6.08)	

PY = Person-years.
CI = Confidence Interval.
*Smear grade at start of treatment:
Smear 3+: Any of the two initial smears was 3+,i.e. >10 acid-fast bacilli (AFB) per 1 high-power field (HPF).
Smear 2+: Any of the two initial smears was 2+,i.e. 1–10 AFB per 1 HPF, but none of them was 3+.
Smear 1+: Any of the two initial smears was 1+,i.e. 10–99 AFB per 100 HPF, but none of them was 2+ or 3+.
†Test for trend.
doi:10.1371/journal.pone.0045724.t001

Table 2. Multivariable analysis of index episode risk factors for subsequent smear-positive tuberculosis re-treatment (N = 1,733).

	Total re-treatment cases	PY	Rate (per 100 PY)	Crude hazard-ratio* (95% CI)	P-value
Treatment outcome					<0.001
Cured	185	8863	2.09 (1.81–2.41)	1	
Completed	14	640	2.19 (1.29–3.69)	1.08 (0.58–2.00)	
Defaulted	92	1341	6.86 (5.59–8.41)	3.97 (3.00–5.26)	
Smear grade†					0.03‡
Smear 1+	35	1588	2.20 (1.58–3.07)	1	
Smear 2+	48	1576	3.05 (2.30–4.04)	1.43 (0.93–2.22)	
Smear 3+	154	4641	3.32 (2.83–3.89)	1.61 (1.11–2.33)	
Age					0.003
0–18	30	758	3.96 (2.77–5.66)	1	
19–39	193	6646	2.90 (2.52–3.34)	0.50 (0.32–0.78)	
40+	68	3430	1.98 (1.56–2.51)	0.40 (0.25–0.65)	

PY = Person-years.
CI = Confidence Interval.
*Adjusted for the other factors shown in the table.
†Smear grade at start of treatment:
Smear 3+: Any of the two initial smears was 3+, i.e. >10 acid-fast bacilli (AFB) per 1 high-power field (HPF).
Smear 2+: Any of the two initial smears was 2+, i.e. 1–10 AFB per 1 HPF, but none of them was 3+.
Smear 1+: Any of the two initial smears was 1+, i.e. 10–99 AFB per 100 HPF, but none of them was 2+ or 3+.
‡Test for trend.
doi:10.1371/journal.pone.0045724.t002

Re-treatment Rates by Treatment Duration and Smear Status Prior to Defaulting

Among the 267 treatment defaulters, 17 (6.4%) defaulted during the intensive phase of treatment. There was an inverse linear association between the time to treatment default (i.e. months of treatment prior to defaulting) and the rate of re-treatment (aHR: 1.87 [95%CI: 0.78–0.97] per one month of treatment; P = 0.01).

Of the treatment defaulters, the sputum smear result at the end of the intensive phase of treatment was negative in 149 (55.8%), positive in 43 (16.1%) and not documented in 75 (28.1%). The rate of smear-positive tuberculosis re-treatment was 5.81 (95% CI: 4.34–7.78) per 100 person-years among defaulters with documented sputum conversion prior to defaulting, 6.07 (95% CI: 3.66– 10.07) with documented positive sputum smear result at follow-up, and 10.00 (95% CI: 7.07–14.14) among treatment defaulters without documented follow-up sputum smear-result. Figure 4 shows the failure function for smear-positive tuberculosis re-treatment by sputum smear status prior to defaulting, adjusted for time to treatment default.

Treatment Outcomes at Re-treatment

Thirty-four (37.0%) of the 92 re-treatment tuberculosis cases who defaulted from treatment at the index episode, defaulted again from re-treatment, compared to 17 (8.5%) of 199 re-treatment cases defaulting after previous cure or treatment completion (Table 3).

Table 3. Treatment outcomes at re-treatment stratified by index episode treatment outcome (N = 291 re-treatment cases).

		Treatment outcome, re-treatment episode					
	Total	Cured/ Completed	Failed	Died	Defaulted	Transfer out	Unknown
Treatment outcome, index episode							
Cured/Completed	199 (100.0%)	152 (76.4%)	12 (6.0%)	8 (4.0%)	17 (8.5%)	2 (1.0%)	8 (4.0%)
Treatment default	92 (100.0%)	49 (53.3%)	3 (3.3%)	2 (2.2%)	34 (37.0%)	3 (3.3%)	1 (1.1%)
Total	**291 (100.0%)**	**201 (69.1%)**	**15 (5.2%)**	**10 (3.4%)**	**51 (17.5%)**	**5 (1.7%)**	**9 (3.1%)**

doi:10.1371/journal.pone.0045724.t003

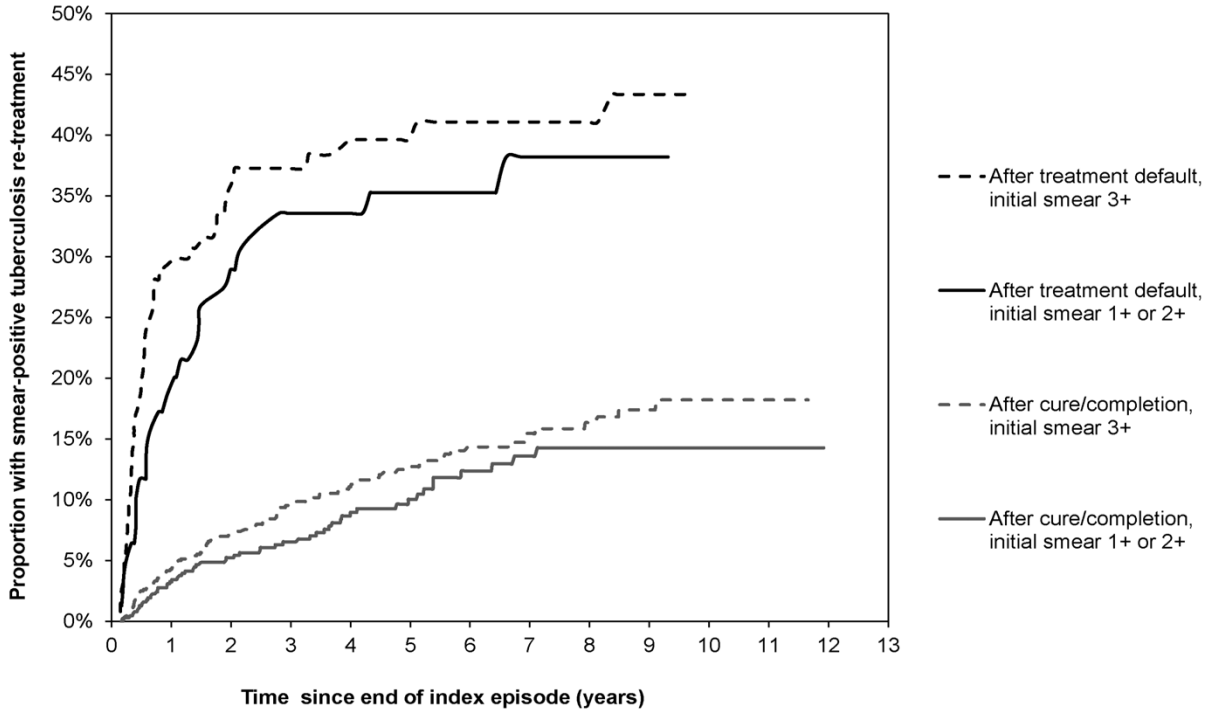

Figure 3. Kaplan Meier failure estimates of re-treatment for smear-positive tuberculosis by index episode sputum smear grading and treatment outcome. doi:10.1371/journal.pone.0045724.g003

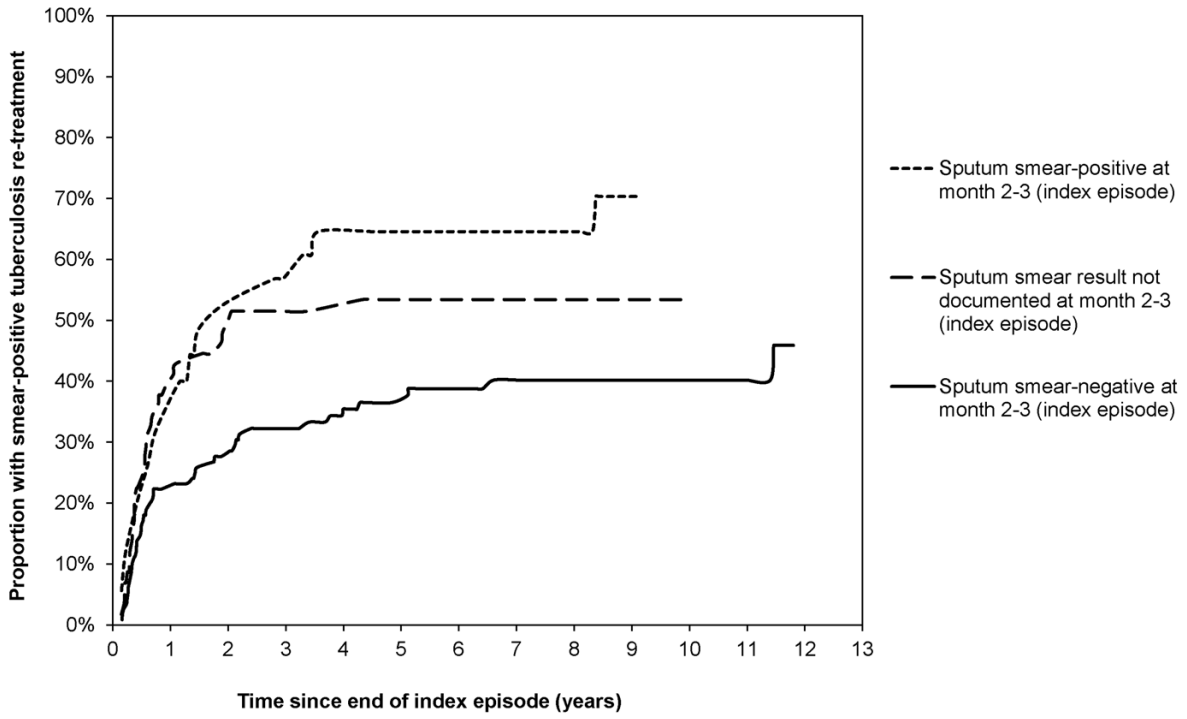

Figure 4. Kaplan Meier failure estimates of smear-positive re-treatment after treatment default, stratified by smear conversion prior to defaulting (adjusted for time to default). doi:10.1371/journal.pone.0045724.g004

Discussion

This study demonstrates for the first time the substantially high rate of smear-positive tuberculosis associated with previous treatment default. Treatment default remains a major risk factor for subsequent smear-positive tuberculosis, even in settings where tuberculosis recurrence due to re-infection is generally common.

The rates of smear-positive tuberculosis presented here are based on treatment records and likely underestimate the true rates of smear-positive tuberculosis after cure, treatment completion and default, because some of the tuberculosis cases might not have returned for treatment or they might have sought treatment elsewhere, and because the population at risk in this study includes those who might have moved or died.

The differences in the rates of smear-positive tuberculosis after treatment default vs. after success are due to the strikingly higher rates within the first two years in those defaulting from treatment. Our results suggest that tuberculosis had been initially contained in the majority of treatment defaulters, i.e. those with longer time to default and with documented smear conversion, and worsened very soon after stopping the treatment. Cases defaulting earlier from treatment and those who continue smear-positive most likely continue to suffer from active disease resulting in high rates of re-treatment within the first two years after defaulting. Absence of smear examination recorded at the end of the initial phase may be a marker of irregular clinic attendance prior to default.

Treatment default is widely considered a risk factor for disease re-activation, but very few studies have looked at rates of tuberculosis after treatment default. A study on re-infection among successfully treated cases in the same communities 1993–1998 documented the frequency of culture confirmed tuberculosis in a sample of previous treatment defaulters for whom strain type information was available, similar to those we found [11]. A study conducted by Vree et al. in rural Vietnam found of 33 treatment defaulters with known outcome, seven had died; only one was found to be culture positive and 23 smear- and culture-negative [21].

The rate of recurrent smear-positive tuberculosis after treatment success corresponds well with previous findings from the Western Cape Province [11] and with reports from late phase clinical trials with a rate of 5.0% at 24 months of follow-up in 282 cases treated in routine public services in Benin, Guinea, Tanzania, Mozambique, Nepal and China, and a rate of 3.8% at 18 months of follow-up in 1,103 cases treated in Guinea, Tanzania, Mozambique, Algeria, Nepal, Vietnam, Bolivia, Colombia and Peru [22,23]. The more constant rate of recurrent episodes after treatment success suggests that recurrence in this group may be more likely due to re-infection, as suggested previously [11,12].

The extent to which smear-positive cases after both, previous default and previous success, maintain the tuberculosis epidemic in this high-burden community cannot be determined from the results of this study. Den Boon et al. previously showed in a prevalence survey conducted in the same setting, that 56% of previously undetected prevalent smear-positive tuberculosis cases had a history of previous treatment [24]. These findings along with the findings of our study support the hypothesis that previously treated cases contribute considerably to the pool of infectious cases in the community.

Although the rate of smear-positive tuberculosis among treatment defaulters is higher, cases after treatment success account for the vast majority of recurrent smear-positive tuberculosis in this setting, a finding that is similar to those reported by Wood et al. in a study using notification data from Cape Town [25]. This is explained by a higher absolute number of successfully treated cases, and a rate of recurrence in this group that is lower in the first two years but constant in the following years.

We did not find evidence in our study that the rate of smear-positive recurrent tuberculosis was higher among HIV co-infected cases. HIV infected individuals may be less likely to be smear-positive upon recurrence and those living with HIV might be more likely to die, reducing the ‘person-years at risk’ which would result in lower rates.

Sputum smear grade at start of treatment was associated with smear-positive recurrence, independent of the later treatment outcome – similar to findings reported by Hesseling et al. in a cohort study from the same community using 24 months follow-up [26]. Tuberculosis cases with a high initial yield of mycobacteria might represent those with more severe, i.e. cavitating disease [27].

Our study has limitations. We made use of probability record linkage in order to identify subsequent episodes of treatment among individuals. Although this method is considered sensitive [28], we might have failed to detect re-treatment episodes of smear-positive tuberculosis in some patients, if for instance women married and changed their surname. Further, the design of our study did not allow us to capture events of subsequent smear-positive tuberculosis untreated or treated elsewhere. The 'population at risk' might have changed according to individuals who died or who moved away from the area. All these factors would have led ultimately to an underestimate of the rates of smear-positive tuberculosis. Rates would have been overestimated if the linkage of episodes was less specific. However, we tried to exclude this possibility by using clear definitions of matches and conducting a careful manual review. We are therefore confident that the rates presented here were unaffected by matching error. Residual confounding might have occurred in our study, given that we were unable to control for other factors known to affect the risk of tuberculosis recurrence, such as smoking, persistent cavities, or undetected drug-resistant disease [29–32].

Further, this study is an evaluation of routine health services based on the information that existed within those services. Such information might be less accurate than information prospectively collected as part of a research project. As noted above, the study did not take into account patients who, for whatever reason, did not return to the health service.

Conclusions

We show for the first time that in a high-burden setting, tuberculosis cases defaulting from their treatment are at high risk of subsequent smear-positive disease. They may thus very likely experience adverse health effects including chronic pulmonary impairment [33], death [34], and acquisition of drug-resistance [35]. Further, they may contribute to the pool of infectious source cases in the community. Moreover, previous defaulters in this setting are at high risk of defaulting again from treatment. There is an urgent need to enhance treatment adherence in order to avoid these untoward events.

Further research is needed to understand to what extent treatment defaulters contribute to overall transmission of tuberculosis within high-burden communities and whether preventing default is an efficient means for reducing tuberculosis transmission. Further, it needs to be determined whether treatment default contributes to the acquisition and transmission of drug resistance in high-burden communities.

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Author Contributions

Analysed the data: FMM RD. Contributed reagents/materials/analysis tools: RD. Wrote the paper: FMM RD DAE NB. Conceived and designed the study: FMM NB DAE. Obtained permission for use of the treatment register data: NB.

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Chapter 3: The temporal dynamics of tuberculosis relapse and reinfection after successful treatment

Overview:

This chapter consists of a published article and reports findings from a study nested in the larger retrospective cohort of smear-positive TB patients treated in the high-incidence setting in suburban Cape Town (Chapter 2). The aim of this study was to investigate, among successfully treated smear-positive TB patients, the relationship between the type of recurrence, i.e. endogenous reactivation (relapse) or exogenous reinfection, and the time to re-treatment for smear-positive TB.

Publication:

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My contribution:

I conceived and designed the study with input from N. Beyers and D.A. Enarson. I collaborated with R. Dunbar and the data management team in data cleaning, consistency checking and validation of the routine TB program data used, and record linkage of individual treatment episodes as well as between treatment episodes and molecular (strain-type DNA) data. I planned and conducted the data analysis, wrote the first manuscript draft, and finalised and submitted the manuscript. R.D. oversaw the data management and record linkage for this study. R.M. Warren and GD van der Spuy led the re-culturing of diagnostic samples, genotyping of *M.tb* strains and RFLP analysis. B.G. Williams contributed to data analysis. All authors contributed to the design of the study, interpretation of the results, and writing/revision of the manuscript draft.

The temporal dynamics of tuberculosis relapse and reinfection after successful treatment

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Abstract

Background. There is increasing evidence from tuberculosis high-burden settings that exogenous reinfection contributes considerably to recurrent disease. However, large longitudinal studies of endogenous reactivation (relapse) and reinfection tuberculosis are lacking. We hypothesize a relationship between relapse vs. reinfection and the time between treatment completion and recurrent disease.

Methods. Population-based retrospective cohort study on all smear-positive tuberculosis cases successfully treated between 1996 and 2008 in a suburban setting in Cape Town, South Africa. Inverse Gaussian distributions were fitted to observed annual rates of relapse and reinfection, distinguished by DNA fingerprinting of Mycobacterium tuberculosis strains re-cultured from diagnostic samples.

Results. Paired DNA fingerprint data were available for 130 (64%) of 203 recurrent smear-positive tuberculosis cases in the 13-year study period. Reinfection accounted for 66 (51%) of 130 recurrent cases overall, 9 (20%) of 44 recurrent cases within the first year, and 57 (66%) of 86 thereafter ($P < .001$). The relapse rate peaked at 3.93% (95% confidence interval [CI], 2.35%–5.96%) per annum 0.35 (95% CI, .15–45) years after treatment completion. The reinfection tuberculosis rate peaked at 1.58% (95% CI, .94%–2.46%) per annum 1.20 (95% CI, .55–1.70) years after completion.

Conclusions. To our knowledge, this is the first study of sufficient size and duration using DNA fingerprinting to investigate tuberculosis relapse and reinfection over a lengthy period. Relapse occurred early after treatment completion, whereas reinfection dominated after 1 year and accounted for at least half of recurrent disease. This temporal relationship may explain the high variability in reinfection observed across smaller studies. We speculate that follow-up time in anti-tuberculosis drug trials should take reinfection into account.

Background

Recurrent tuberculosis after successful treatment constitutes a challenge to tuberculosis control, particularly in populations with a high prevalence and with high rates of human immunodeficiency virus (HIV) coinfection. The question whether recurrent tuberculosis is due predominantly to endogenous reactivation (relapse) or exogenous reinfection has been a subject of debate for decades [1]. Models have suggested that the contribution of reinfection increases with the incidence of tuberculosis and risk of infection in the particular setting [2–4].

DNA fingerprint technologies [5] have been used to differentiate between relapse and exogenous reinfection. Re-infection seems to be an important [6, 7] and even major [8, 9] underlying cause of recurrent tuberculosis in high-burden settings. However, studies have yielded conflicting evidence, with the proportion of reinfection tuberculosis ranging from 0% to 100% in studies conducted in earlier years (ie, 1993–2001) [10]. At least 2 studies in more recent years concluded that reinfection was not a common cause of disease recurrence in a high-burden setting [11, 12]. Thus, the actual extent to which re-infection contributes to recurrent tuberculosis after successful treatment remains uncertain. There is more consistent evidence that reinfection rather than relapse may explain high rates of disease recurrence observed among individuals co-infected with HIV [13–15]. Longitudinal studies of relapse and reinfection tuberculosis in high-burden settings have been limited, because they depend on lengthy follow-up and sample availability. Given that small studies may be subject to sampling bias [16], large longitudinal studies are needed to better clarify the contribution and timing of relapse and reinfection to recurrent tuberculosis [10, 17]. Better knowledge about the timing of relapse and reinfection may be of value for the design of anti-tuberculosis drug trials, which usually do not take reinfection into account. At least 2 of the current large phase 3 anti-tuberculosis drug trials rely on 24-month post-treatment follow-up for their primary outcome [18, 19].

We conducted a large longitudinal study in a tuberculosis high-burden setting with known high rates of recurrent disease [20]. Recurrent tuberculosis contributes significantly to the overall burden of tuberculosis in the area, irrespective of its association with HIV [21]. The purpose of our study was to investigate, among successfully treated smear-positive tuberculosis cases, the relationship between the type of recurrence—that is, endogenous reactivation (relapse) or exogenous reinfection— and the time to recurrent smear-positive tuberculosis.

Methods

Study Setting

The study was conducted in a suburban area in Cape Town, South Africa, covering 3.4 km², with approximately 39 000 inhabitants of low socioeconomic status [22]. The directly observed treatment, short-course (DOTS) strategy [23] was introduced in 2 primary health care clinics in 1996. Treatment was supervised daily by health care staff in the clinics or in the community by trained health care workers. Treatment outcomes were documented according to standard definitions [24]: cure, for patients who were smear negative at or 1 month before the completion of treatment and on ≥1 previous occasion; or treatment completed, for patients who had completed treatment but without proof of cure because smear results were unavailable. The term treatment success includes both cure and treatment completed.

Study Design

The study was nested in a retrospective cohort study [20] conducted among all patients with smear-positive tuberculosis receiving standard first-line treatment documented in the local treatment registers who either successfully completed or defaulted from treatment between 1996 and 2008. The underlying study used routinely collected treatment register data to investigate the frequency of retreatment for smear-positive tuberculosis by previous treatment outcome [20].

The present study included all patients with smear-positive tuberculosis who successfully completed their index treatment episode (documented cure or treatment completed) and were subsequently treated again for sputum smear-positive tuberculosis. Any recurrent smear-positive treatment episode recorded from the first day after the index treatment episode had been completed was considered, as recommended by Lambert et al [10]. The principal determinant was the type of recurrence (ie, relapse or reinfection), and the main outcome was the time to retreatment for smear-positive tuberculosis.

Ascertainment of Relapse and Reinfection

Sputum samples used for this study were routinely collected from all patients, processed in the routine laboratory, and subsequently transported to the research laboratory for culture and genotypic analysis. Decontaminated samples were cultured in BACTEC460, MGIT 960 or Löwenstein-Jensen medium for DNA extraction [25]. Isolates were classified using the internationally standardized IS6110 DNA fingerprinting method [5]. Each DNA fingerprint was entered into a GelCompar database and analysed using GelCompar software (version 6.5). For each case included in the study, we identified diagnostic samples collected for both, the index treatment and the recurrent episode. A diagnostic sample was defined as the first chronological sputum sample with a sample date between 2 months before and 2 months after the onset date of the corresponding treatment episode.

Paired DNA fingerprint patterns (i.e. from the index and recurrent treatment episodes for the same individual) were compared on the basis of their restriction fragment length polymorphism patterns using UPGMA (Unweighted-pair group method with arithmetic mean) and the Dice coefficient. Relapse was inferred when both patterns either were identical or differed by only 1 or 2 bands, provided that an identical strain pattern was not identified in a sample of another case before the corresponding treatment episode of the patient (implying an intra-patient evolutionary event) [26]. Reinfection was inferred if paired samples did not meet the definition for relapse. Previous studies from this laboratory have shown that laboratory error and cross-contamination were on the order of 2.1% [8, 27]. To investigate the possibility of rifampicin drug resistance at baseline and recurrence, DNA sequencing for rpoB genotype mutation was conducted for all diagnostic samples.

Time to Recurrence

The time to recurrence was defined as the time between the documented end date of the index treatment episode and the date when the recurrent treatment episode was recorded. In a few cases with missing dates, the end date was identified via a patient folder search.

Data Analysis

Survival analysis was used to compare the distributions of relapse and reinfection tuberculosis cases over time since treatment completion. The Kolmogorov-Smirnov test was used to test for a difference in the observed distributions. Annual rates of relapse and reinfection tuberculosis were calculated by dividing the number of relapse and reinfection cases by the population at risk at quarterly (3-month) intervals, assuming that the proportion of relapse and reinfection cases observed at each time interval would not differ between recurrent cases with and without ascertained type of recurrence. Inverse Gaussian functions [28] were fitted to the observed annual rates to estimate the trends in relapse and reinfection tuberculosis over time. Sensitivity analysis was conducted by including smear-negative/culture-positive recurrent episodes in the analysis.

Ethics Statement

The study was approved by the Committee for Human Research, Faculty of Medicine and Health Sciences, Stellenbosch University (N09/05/144 and amendments 1 and 3).

Results

A total of 2359 cases with an index episode of treatment for smear-positive tuberculosis were recorded in the treatment registers, of whom 1869 (79.2%) were successfully treated (1743 were cured, 126 completed treatment). A recurrent episode of treatment for smear-positive tuberculosis after the index episode was recorded for 203 (10.9%) of 1869 successfully treated

cases. Figure 1 illustrates cases included in and excluded from the study. The median time to smear-positive retreatment was 21 months (interquartile range [IQR], 8–48 months). Two of the 203 recurrent cases had been classified as cured/treatment completed at the index treatment episode despite having a positive sputum smear result documented at the end of treatment, but in both cases the smear result was classified as "scanty."

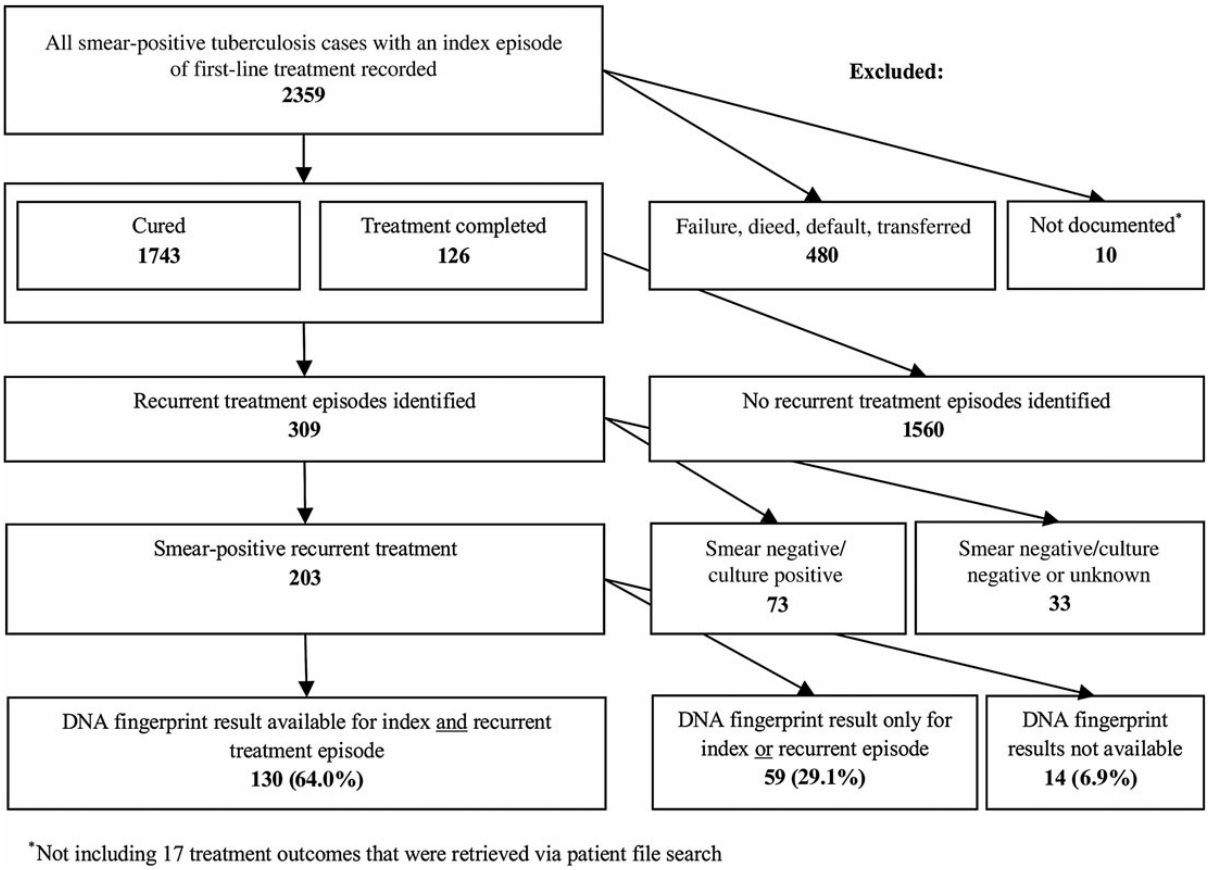

Figure 1. Overview of tuberculosis cases included in and excluded from the study.

Completeness of Paired DNA Fingerprint Results

For 130 (64%) of the 203 recurrent smear-positive cases, a DNA fingerprint result was available for both the diagnostic sample collected at the index episode and that collected at the recurrent episode (Table 1). Availability of both results was associated with the calendar year of treatment completion (P = .03). There was no association between the time to recurrence and availability of both DNA fingerprint results (P = .63). The median time to recurrence was 20.4 months (IQR, 9.0–45.5 months) in recurrent cases with both results available vs. 24.8 months (IQR, 6.1–53.7 months) in recurrent cases with ≥1 result missing (P = .92).

Relapse and Reinfection Tuberculosis

Of the 130 recurrent smear-positive tuberculosis cases with both DNA fingerprint results available, 64 (49%) were relapse cases and 66 (51%) reinfection tuberculosis cases (Table 2). Reinfection accounted for 9 (20%) of 44 recurrent cases within the first year, and 57 (66%) of 86 recurrent cases thereafter. After >2 years 43 (72%) of 60 recurrent cases were due to reinfection (Table 2). There was a strong association between relapse and earlier recurrence (Kolmogorov-Smirnov test for difference in the observed distributions, P < .001; Figure 2).

The association between relapse, reinfection, and the time to recurrence remained after the analysis was restricted to cases after cure (66% relapse within 2 years vs. 27% later than 2 years; P < .001) and after it was restricted to 82 recurrent cases with a documented HIV-negative test result (59% relapse within 2 years vs. 21% later than 2 years; P = .02). Ten of 100 patients with documented HIV-positive tuberculosis had an episode of recurrent smear-positive tuberculosis. DNA fingerprint results were available in 7, of whom 6 had relapse cases.

Table 3 compares characteristics between patients with relapse or reinfection tuberculosis and those without recurrent treatment. None of the index episode diagnostic samples and 2 of the 130 recurrent episode samples (1.5%), 1 relapse and 1 reinfection, were found to be positive for *rpoB* mutation.

Annual Rates of Recurrent Tuberculosis Due to Reinfection and Relapse

The relapse rate peaked at 3.93% (95% confidence interval [CI], 2.35%–5.96%) per annum 0.35 (95% CI, .15–.45) years after completion of treatment, followed by a steady decline (Figure 3). The reinfection tuberculosis rate peaked at 1.58% (95% CI,.94%–2.46%) per annum 1.20 (95% CI, .55–1.70) years after with the calendar year of treatment completion (P = .03). There was no association between the time to recurrence and availability of both DNA fingerprint results (P = .63). The median time completion of treatment (Figure 3). Table 2 summarizes numbers and annual rates of recurrent, relapse and reinfection tuberculosis cases.

Sensitivity Analysis: Smear-Negative, Culture Positive Recurrent Episodes

Including smear-negative/culture-positive recurrent episodes in the analysis did not change the observed association between relapse, reinfection and the time to recurrence. Of 276 recurrent cases confirmed by either smear or culture, 159 (58%) had DNA fingerprint results available for both the index and the recurrent treatment episode. Of these, 82 (52%) were relapse cases, of which 54 (66%) were treated again within 2 years, compared with only 26 (34%) of 77 reinfection cases (P < .001).

Mixed Strain Infection at the Index Episode

Two different strains of M. tuberculosis were detected at the index episode in 2 of the 130 recurrent cases. At recurrence, both were classified as reinfection according to the study definition. However, for both, the single strain found at the recurrent episode was equal to the underlying strain at the index episode (all rpoB wild-type infections).

Table 1. Index Episode Characteristics in Patients With Recurrent Tuberculosis With Both DNA Fingerprint Results Available (Index and Recurrent Episode) and Those With ≥1 DNA Fingerprint Result Unavailable

Characteristic	Total No.	DNA Fingerprint Result for ≥1 Episode Missing	DNA Fingerprint Results for Both Episodes Available	*P* Value
		No. (Row %)	No. (Row %)	
Overall	203	73 (36.0)	130 (64.0)	. . .
Sex				.07
Female	75	33 (44.0)	42 (56.0)	
Male	128	40 (31.2)	88 (68.8)	
Age, y				.76
0–18	21	6 (28.6)	115 (71.4)	
19–39	127	47 (37.0)	80 (63.0)	
≥40	55	20 (36.4)	35 (63.6)	
Patient category				.20
New	133	52 (39.1)	81 (60.9)	
Retreatment	70	21 (30.0)	49 (70.0)	
HIV status				.90
Negative	82	29 (35.4)	53 (64.6)	
Positive	10	3 (30.0)	7 (70.0)	
Unknown/ missing	111	41 (36.9)	70 (63.1)	
Initial smear grade				.05
Smear 1+	26	13 (50.0)	13 (50.0)	
Smear 2+	33	10 (30.3)	23 (69.7)	
Smear 3+	108	32 (29.6)	76 (70.4)	
Smear positive (unknown grade)	36	18 (50.0)	18 (50.0)	
Smear conversion				.58
Yes (negative at month 2)	149	52 (34.9)	97 (65.1)	
No (positive at month 2)	43	18 (41.9)	25 (58.1)	
Unknown	11	3 (27.3)	8 (72.7)	
Treatment outcome				.44
Cured	188	69 (36.7)	119 (63.3)	
Completed	15	4 (26.7)	11 (73.3)	
Treatment end (year)				.03
1996–1999	47	20 (42.6)	27 (57.4)	
2000–2003	82	35 (42.7)	47 (57.3)	
2004–2008	74	18 (24.3)	56 (75.7)	
Time of recurrent episode (after end of index episode)				.63[a]
1st year	67	23 (34.3)	44 (65.7)	
2nd year	39	13 (33.3)	26 (66.7)	
3rd year	28	11 (39.3)	17 (60.7)	
4th year or later	64	24 (37.5)	40 (62.5)	

Abbreviation: HIV, human immunodeficiency virus.

[a] Test for trend.

Table 2. Smear-Positive Recurrence, Relapse, and Reinfection Tuberculosis Among 1869 Successfully Treated Patients, 1996–2008

Category	Total	Year 1	Year 2	Year 3	Year 4	Year 5+
Recurrent cases, No. (%)	203	67 (33)	39 (19)	28 (14)	20 (10)	51 (25)
Recurrent cases with DNA fingerprint data, No. (%)	130	44 (34)	26 (20)	17 (13)	16 (12)	27 (21)
Due to relapse	64	35 (55)	12 (19)	4 (6)	5 (8)	8 (13)
Due to reinfection	66	9 (14)	14 (21)	13 (20)	11 (17)	19 (29)
Incidence risk of recurrence[a]	. . .	3584	2164	1578	1140	. . .
Incidence risk of relapse[a] (95% CI)	. . .	2836 (2131–3693)	998 (593–1574)	371 (158–811)	342 (126–743)	. . .
Incidence risk of reinfection tuberculosis[a] (95% CI)	. . .	733 (410-1253)	1165 (723–1776)	1184 (734-1804)	798 (437–1336)	. . .

Abbreviation: CI, confidence interval.

[a] Per 100 000 successfully treated cases.

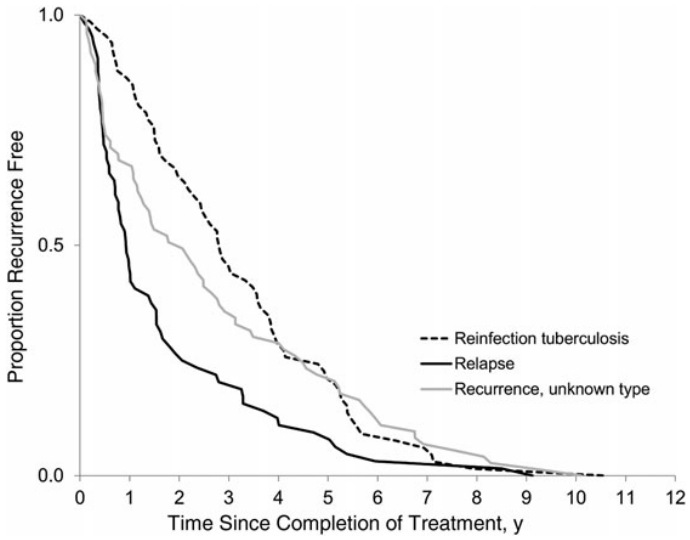

Figure 2. Kaplan-Meier survival estimates for relapse (n = 64), reinfection tuberculosis (n = 66), and unknown type of recurrence (n = 73) (Kolmogorov-Smirnov test for difference in relapse vs reinfection, P < .001).

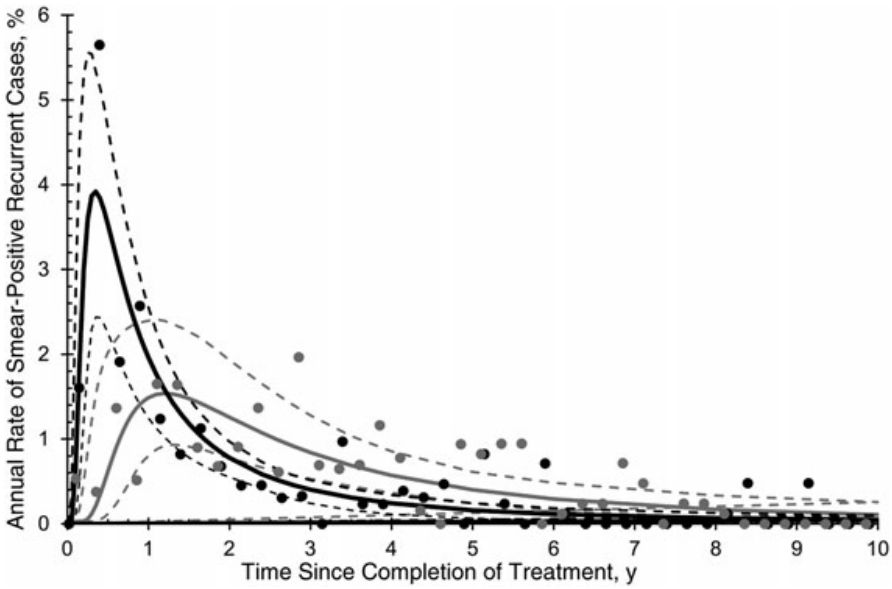

Figure 3. Smear-positive tuberculosis incidence (percentage per annum) as a function of time since successful completion of treatment. Black represents relapse; grey: reinfection tuberculosis; solid lines: fitted inverse Gaussian functions; dashed lines: 95% confidence intervals

Table 3. Index Episode Characteristics in Patients With a Subsequent Episode of Smear-Positive Tuberculosis Due to Relapse and Reinfection and Patients Without Recurrence

Characteristic	Confirmed Smear-positive Recurrence, No. (%)			No Recurrence, No. (%)[a]	*P* Value for Difference	
	Unknown Mode	Relapse	Reinfection		Relapse vs No Recurrence	Reinfection vs No Recurrence
Overall	73	64	66	1560	. . .	. . .
Sex					.19	.048
Female	33 (45.2)	22 (34.4)	20 (30.3)	664 (42.6)		
Male	40 (54.8)	42 (65.6)	46 (69.7)	896 (57.4)		
Age, y					.30	.46
0–18	6 (8.2)	8 (12.5)	7 (10.6)	132 (8.5)		
19–39	47 (64.4)	39 (60.9)	41 (62.1)	889 (57.1)		
≥40	20 (27.4)	17 (26.6)	18 (27.3)	536 (34.4)		
Patient category					.88	.004
New	52 (71.2)	45 (70.3)	36 (54.6)	1108 (71.2)		
Retreatment	21 (28.8)	19 (29.7)	30 (45.5)	449 (28.8)		
HIV status					.06	.32
Negative	29 (39.7)	26 (40.6)	27 (40.9)	739 (47.4)		
Positive	3 (4.1)	6 (9.4)	1 (1.5)	73 (4.7)		
Unknown/missing	41 (56.2)	32 (50.0)	38 (57.6)	748 (47.9)		
Initial smear grade					.01	.18
Smear 1+	13 (17.8)	3 (4.7)	10 (15.2)	289 (18.5)		
Smear 2+	10 (13.7)	14 (21.9)	9 (13.6)	269 (17.2)		
Smear 3+	32 (43.8)	39 (60.9)	37 (56.1)	727 (46.6)		
No data	18 (24.7)	8 (12.5)	10 (15.2)	275 (17.6)		
Smear conversion					.17	.32
Yes (negative at month 2)	52 (71.2)	49 (76.6)	48 (72.7)	1253 (80.3)		
No (positive at month 2)	18 (24.7)	11 (17.2)	14 (21.2)	236 (15.1)		
No data	3 (4.1)	4 (6.3)	4 (6.1)	71 (4.6)		
Treatment Outcome					.17	.88
Cured	69 (94.5)	57 (89.1)	62 (93.9)	1458 (93.5)		
Completed	4 (5.5)	7 (10.9)	4 (6.1)	102 (6.5)		

Abbreviation: HIV, human immunodeficiency virus.

[a] The "no recurrence" category includes patients without any recurrent treatment episode identified (excluding those with smear-negative recurrent episodes).

Discussion

This is the first longitudinal study of sufficient duration and size to investigate relapse and reinfection in relation to the time to recurrent smear-positive tuberculosis. Relapse occurs predominantly in the first year, whereas reinfection tuberculosis predominates over the subsequent years after successful treatment. The delayed appearance of reinfection tuberculosis is plausible, given that the risk of reinfection is related to the disease burden in the community, and there is a lag-time period between infection and progression to disease.

Our results are consistent with findings from the earlier British Medical Research Council trials, which showed that the majority of relapse cases would occur within 6–12 months of treatment [29, 30], notably without being able to distinguish between relapse and reinfection. Our results are also consistent with those of studies from South Africa [13, 15] and China [31] indicating that relapse predominated in patients with early recurrence, whereas reinfection was associated with longer intervals between tuberculosis episodes.

Our results have implications for studies of relapse and reinfection tuberculosis in high-burden populations. Time-of-observation bias is likely for retrospective analyses of clinical trials, which usually rely on relatively short follow-up periods, favouring higher proportions of relapse, as observed recently in a large retrospective analysis in Uganda [12]. Furthermore, sampling bias may occur in retrospective studies if the sample of patients was small and not representative of all recurrent cases. Variation in follow-up or observation time and, consecutively, in the time

to recurrent tuberculosis may thus serve to explain the high variability in the contribution of relapse and reinfection observed across studies [10].

Our results have implications for clinical trials. We show that reinfection was the dominant cause of recurrent tuberculosis soon after the first year since treatment completion. Phase 3 anti-tuberculosis drug trial designs may thus benefit from shortening of follow-up time in order to avoid the undesired “contaminating” effect of reinfection tuberculosis. This is in accordance with previous recommendations based on recurrence rates in the earlier British Medical Research Council trials [30, 32].

We show that, in a high-burden setting, recurrence of smear-positive tuberculosis after treatment success may be due to reinfection in at least half of all recurrent cases. Two prior studies conducted in the area concluded that exogenous reinfection was the major cause of tuberculosis after cure and that the rate of reinfection tuberculosis exceeded that of new tuberculosis cases [8, 9]. Both studies were limited by the small number of patients studied, and neither took into account the time to recurrence.

Although the overall risk of relapse may be reduced by provision of standardized and supervised treatment, the increased risk of reinfection in high-burden settings exacerbates the burden of recurrent tuberculosis. Thus, successfully treated cases, as well as treatment defaulters [20], represent an important risk group in tuberculosis high-burden settings, a point worth considering in screening and active case finding strategies.

It remains uncertain to what extent previously treated cases contribute to tuberculosis transmission within communities. den Boon et al [33] reported that previously treated individual represented more than half of patients with prevalent smear-positive tuberculosis. Both their and our study took place in a community where tuberculosis rates remain constantly high, >10 years after the introduction of the internationally recommended control strategy. The strength of our study is the large sample of recurrent tuberculosis cases, sufficient to study relapse and reinfection tuberculosis in a high-burden setting over a lengthy period.

Our study has limitations. We used a programmatic definition of treatment success on the basis of routinely documented information. The source and availability of data did not enable us to describe clinical and biological mechanisms underlying relapse and reinfection tuberculosis. In particular, we were unable to exclude the possibility of drug resistance beyond rpoB genotype results at treatment initiation or to describe acquisition of drug resistance during treatment as a potential cause of relapse.

Both DNA fingerprint results were available in 64% of all recurrent cases – a higher proportion than in earlier studies. Availability was lower in patients treated in earlier years and with lower sputum smear grades, which may relate to the probability of bacteria survival and successful re-culturing. We did not observe an association between availability and time between both treatment episodes; it is therefore unlikely that selection bias explains the observed temporal distributions of relapse and reinfection.

Using retreatment probably underestimated true rates of disease recurrence. Some patients with recurrent disease might not have returned for treatment or sought treatment elsewhere, and the population at risk in this study includes those who moved or died. Time to retreatment involves not only the time to recurrent disease but also time to diagnosis and treatment.

The definition of relapse and reinfection was based on comparison of *M. tuberculosis* DNA fingerprint patterns using restriction fragment length polymorphism analysis, the state of the art method when this study was conducted. More advanced methods, such as whole genome sequencing, may be more powerful for discriminating different strains, but they were beyond the scope of our study. Lower discriminative power may have led to an underestimation of reinfection but is unlikely to explain the observed temporal distributions.

Although strain diversity is known to be high in this area [34], individuals may have been re-infected within clusters of the same strain, for example, after being repeatedly exposed in the household or in social networks. Conversely, mixed-strain infections [35, 36] may have led to misclassification: Rather than reinfection, a selection process of the underlying strain may

have led to recurrent disease in individuals with mixed-strain infection, particularly if the underlying strain was drug resistant.

We conducted our study in a setting where HIV coinfection is less common than in other high-burden settings. Low numbers of co-infected patients with recurrent tuberculosis precluded any rate estimates for this subgroup. Settings with more frequent HIV coinfection may have higher overall rates of reinfection [15, 37, 38] and shorter time to relapse and reinfection. Furthermore, the frequency and timing of reinfection tuberculosis may vary across settings with a high vs. low annual risk of infection.

Future research should serve to improve our understanding of programmatic and individual risk factors for relapse and re-infection tuberculosis. A more comprehensive model of strain persistence and repeated infections that takes into account mechanisms such as treatment adherence, mixed infections, and acquisition of drug resistance would be valuable. Reducing relapse and reinfection tuberculosis may be an important means of reducing the overall tuberculosis burden in high-prevalence settings.

Notes

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Chapter 4: Modelling the impact of tuberculosis control interventions targeted to previously treated people in a high-incidence setting

Overview:

This chapter consists of a manuscript that was submitted for publication. It reports the findings of a study using a transmission-dynamic mathematical model of TB and HIV that was calibrated to data from the same high-incidence setting in suburban Cape Town (Chapters 2 and 3). The aim of this study was to project the population-level impact of two control interventions, targeted active TB case finding (TACF) and secondary isoniazid preventive therapy (2°IPT) among people who previously completed TB treatment on TB incidence and mortality in the local population.

My co-authors:

Reza Yaesoubi, Nicolas A. Menzies, Joshua A. Salomon, Alyssa Bilinski, Nulda Beyers, Ted Cohen

My contribution:

I conceived the study together with T. Cohen. I wrote the study protocol, developed the model structure, collected the data, and specified parameter values and calibration targets with input from all authors. I contributed to model implementation and parameterization. I wrote the first manuscript draft, finalised and submitted the manuscript for publication. R. Yaesoubi implemented the model and analysed the data. N. Beyers contributed to data collection. All authors contributed to the study design, development of the model structure, interpretation of the results, and writing/revision of the manuscript.

Note:

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Modelling the impact of tuberculosis control interventions targeted to previously treated people in a high-incidence setting

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(Submitted manuscript)

Abstract

Background. In high-incidence settings, previously treated individuals contribute substantially to the burden of incident and prevalent tuberculosis (TB). The extent to which interventions targeted to this high-risk group can improve TB control has not been established. We aimed to project the population-level impact of control interventions targeted to individuals with a history of previous TB treatment in a high-incidence setting.

Methods. We developed a calibrated, transmission-dynamic model of TB in two communities in suburban Cape Town, South Africa. We projected the impact of (1) annual targeted active TB case finding (TACF) among all individuals who had previously completed TB treatment and (2) TACF combined with lifelong secondary isoniazid preventive therapy (2°IPT).

Findings. We project that under current control efforts, the TB epidemic will remain in slow decline for at least the next decade in this setting. Additional interventions targeted to previously treated people could greatly accelerate these declines. We project that annual TACF combined with 2°IPT among those who completed a prior episode of TB treatment would avert 40% (95% uncertainty interval: 20%; 59%) of incident TB cases and 41% (16%; 62%) of TB deaths occurring between 2016 and 2025.

Interpretation. In this high-incidence setting, TACF and 2°IPT among previously treated individuals could accelerate declines in TB morbidity and mortality. Studies to measure the cost and resource implications of these interventions are needed to establish the feasibility of this type of targeted approach for improving TB control in different settings.

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Introduction

Worldwide, an estimated 10.4 million people developed tuberculosis (TB) and 1.8 million deaths were attributable to the disease in 2015 [1]. Substantial innovation in TB control is needed to reach the targets of the new global End TB Strategy, which aims to eliminate TB by the year 2035 [2]. Rates of TB decline must accelerate in settings with the highest incidence of TB, some of which are located in southern Africa and facing the dual burden of TB and human immunodeficiency virus (HIV) [3]. In these settings, the prevalence of untreated TB remains high, and conventional control approaches that rely on passive case finding may fail to identify infectious cases early enough to prevent transmission [4-6].

Active and enhanced case finding and wide-scale use of preventive therapy have been considered as enhanced activities for improving TB control, but these approaches will require substantially increased budgets. Furthermore, disappointing results from community-randomized trials of population-wide case finding and preventive therapy interventions [7,8] have tempered enthusiasm for untargeted use of these interventions. It remains unknown whether targeting of case finding and preventive therapy to high risk groups could be an

effective approach for disease control in communities. The broader impact of a targeted approach depends on whether it is possible to prevent disease or reduce the duration of infectiousness for an easily identifiable subgroup that experiences a high relative risk of disease and is responsible for a substantial fraction of transmission.

One subgroup that may be attractive for targeted interventions includes individuals with a history of previous TB treatment [9]. Studies from Southern Africa show a high incidence of recurrent TB even after previous successful treatment [10-13], resulting from both endogenous reactivation and exogenous reinfection [14]. We recently documented a large burden of prevalent TB among previously treated adults in 24 high TB burden communities in Southern Africa consistent with the hypothesis that this risk group drives a substantial fraction of transmission in these settings [15].

In this study, we use a dynamic mathematical model to project the impact of two targeted control interventions, targeted active case finding (TACF) and secondary isoniazid preventive therapy (2°IPT) among individuals who previously completed TB treatment in a high-incidence setting in suburban Cape Town, South Africa. We estimated the impact of these targeted interventions on TB incidence, prevalence, and mortality over a 10-year period.

Methods

Modeling approach

We developed a stochastic compartmental transmission-dynamic model of the TB and HIV epidemic in a high-incidence setting in suburban Cape Town, South Africa (see Supplementary information document for details about the study setting). The model follows the conventions of earlier TB models [16-20], with additional structure to distinguish between individuals who were never before treated for TB (treatment-naïve) and those who were previously treated for TB (treatment-experienced). We allow that treatment-experienced individuals may differ from treatment-naïve individuals because they experience higher risk of infection or higher risk of progression to active disease following infection. The model includes a main component for adults aged ≥15 years (Figure 1) and a simplified subcomponent for children aged 0-14 years. We implemented four model subdivisions to account for HIV infection, progression and provision of antiretroviral treatment (ART) in our setting. Full model details are provided in the Supplementary information document.

Parameter estimation and model calibration

Parameters were estimated based on previous studies or informed by model calibration. We calibrated our model to data from the study setting, describing local demography, TB prevalence among treatment-naïve and treatment-experienced individuals, TB case notifications and treatment outcomes and estimates of HIV prevalence. We used a Bayesian posterior estimation approach for calibration [21]. Here, parameter sets were randomly selected from prior distributions, and the goodness of fit of resultant projections to the calibration data was evaluated. Parameter sets were then resampled to produce final results, with the probability of selection determined by the goodness of fit to the calibration data. A detailed description of epidemic parameters and their ranges, calibration procedure, model initialization and simulation approach are provided in the Supplementary Information Document. Calibration targets and sampled model trajectories are shown in Figure 2.

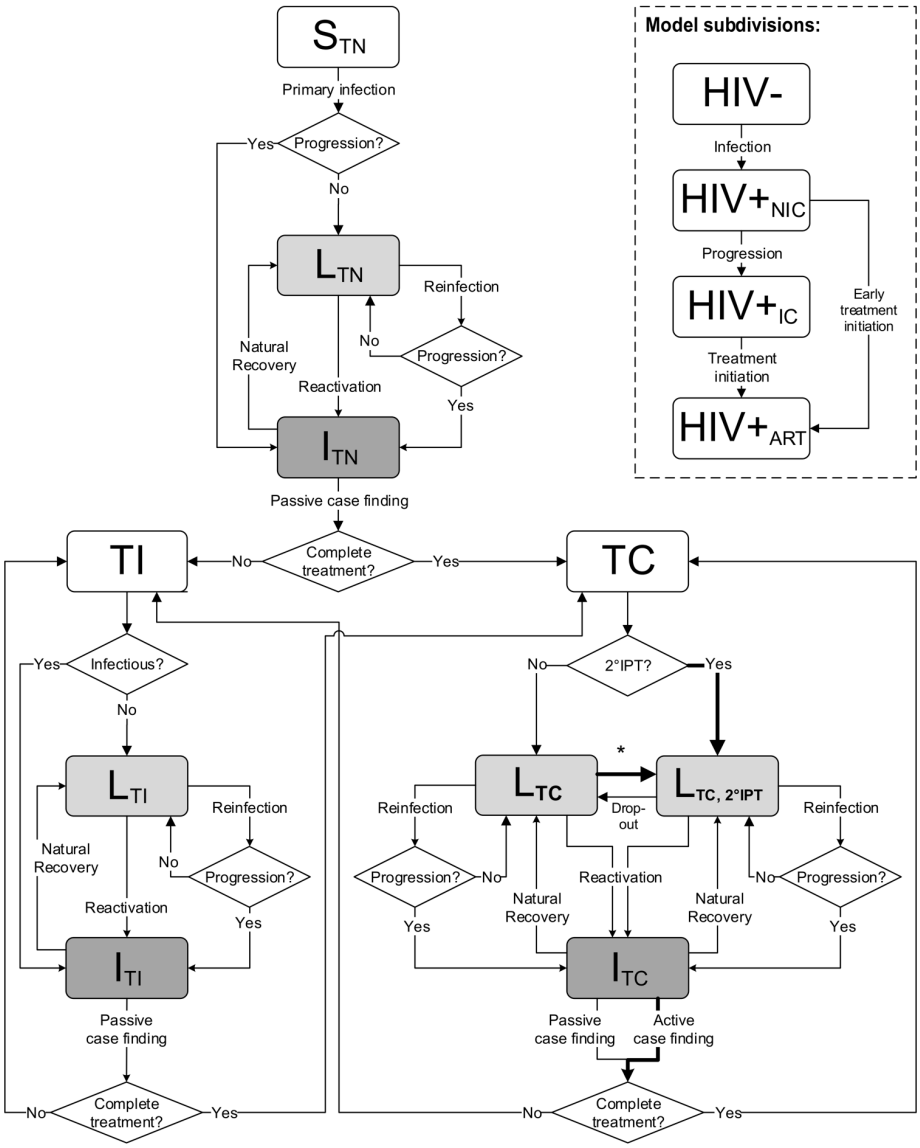

Figure 1. Structure of the mathematical model
Compartments: *S = Susceptible; L = Latently infected; I = Infectious; TI = Treatment that remains incomplete; TC = Treatment that is completed;* Subscripted annotations: *TN = TB treatment-naïve; TC = after prior complete treatment; TI = after prior incomplete treatment; 2°IPT = Secondary isoniazid preventive therapy;* Transitions not shown: mortality rates, transitions from childhood subcomponent (see *Supplementary Information Document*), and transitions across HIV subdivisions (see Fig. 2); Bold arrows: modeled interventions, * denotes 2°IPT offered to disease-free individuals after complete treatment during the first intervention year (2016); Model subdivisions in the upper right box: *HIV- = HIV uninfected; HIV+ = HIV infected;* Subscripted annotations: *NIC = non-immunocompromised (CD4 cell count >350 cells per mm³); IC = immunocompromised (CD4 ≤ 350); ART = on antiretroviral treatment*

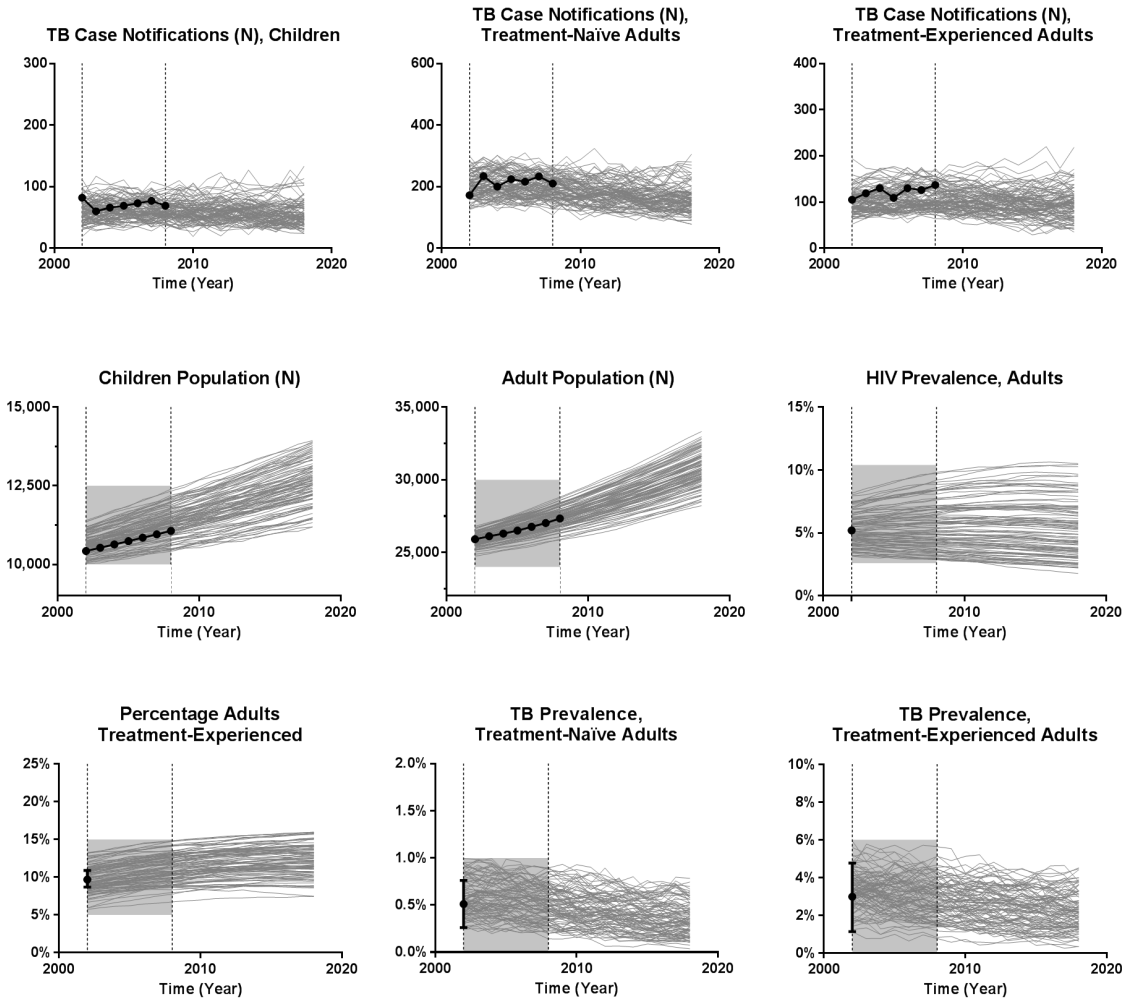

Figure 2. Overview of calibration targets and fitted model trajectories
The nine calibration targets are shown as bold black dots, with error bars representing 95% confidence intervals where applicable; a subset of 100 randomly selected model trajectories are shown as grey lines, and a pre-specified feasible range as shaded area; the interval between the dotted vertical lines shows the model calibration period (2002 - 2008); a complete list of calibration targets is provided in the *Supplementary Information Document*

Interventions

We projected the impact of the following two targeted interventions.

Targeted active TB case finding (TACF). We assumed that all adults who previously completed TB treatment were re-evaluated for active TB on average once per year and referred for TB treatment. For individuals who had numerous episodes of TB treatment, TACF was restricted to individuals who completed their most recent episode of TB treatment (Figure 1).

Secondary isoniazid preventive therapy (2°IPT). In the first year of intervention, we modeled a catch-up 2°IPT campaign that reached 90% of individuals with previously completed TB treatment in the population. Subsequent to this catch-up period, we assumed that 2°IPT was offered to individuals following completion of a full course of TB treatment and that an average of 90% of individuals completing treatment were enrolled. We allowed the effectiveness of

2°IPT in preventing recurrent disease due to reinfection or reactivation to vary between 45% and 85%, a range informed by two prior studies [22,23]. 2°IPT was intended as a lifelong intervention, but we assumed that on average 15% of people drop-out per year, and that the protective effect of 2°IPT was lost at the cessation of treatment [24].

Model outcomes and data analysis

We projected trends in TB incidence, prevalence and mortality for ten consecutive years, 2016 to 2025, under the baseline scenario and under two interventions scenarios: 1) TACF alone and 2) TACF plus 2°IPT. The impact of these intervention scenarios was defined as the cumulative number of TB cases and deaths that was averted during the 10-year period (2016 - 2025) relative to the baseline scenario. We also conducted sensitivity analysis to explore the impact of different periodicities of TACF (6 vs. 12 and 24 months on average) and probabilities of 2°IPT enrolment (none vs. 50%, 75% and 90%) after completion of TB treatment. Detailed information about definitions and methods of estimating model outcomes are provided in the Supplementary Information Document.

Role of the funding source

The funders of the study had no role in study design data collection, data analysis, data interpretation, or writing of the report. FMM, RY and NB had full access to the calibration data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Projections under the baseline scenario

We estimate that in 2016, 13% (95% uncertainty interval: 9%; 17%) of all adults had previously been treated for active TB. The estimated prevalence of untreated TB was 2.2% (0.7%; 4.3%) among treatment-experienced adults, 5.5-fold higher than among treatment-naïve adults (0.4% [0.1%; 0.7%]). The model allowed that differential prevalence among treatment-naïve and treatment-experienced individuals may result from an increased risk of productive infection and an increased risk of reactivation among individuals with a prior treatment episode. Posterior distributions of key parameters of the natural history of TB for treatment-experienced and -naïve individuals are provided in the Supplementary Information Document (S7).

In the absence of targeted interventions, we projected a total of 4,292 (2,285; 7,155) incident TB cases and 642 (266; 1,190) TB-associated deaths between 2016 and 2025. In this time period, 1,525 (607; 2,744) incident TB cases will occur among adults who had completed a prior episode of treatment, representing 35% (22%; 46%) of all incident cases.

Among treatment-naïve adults, TB incidence per 100,000 people was 871 (496; 1,404) in 2016 and will decline to 717 (345; 1,289) by 2025. TB incidence among treatment-experienced adults was 4,089 (1,843; 6,353) per 100,000 people in 2016, 5.7-times higher than among treatment-naïve adults, and will decline to 3,594 (1,331; 5,763) by 2025. The projected average annual decline in TB incidence between 2016 and 2025 was 2.0% among treatment-naïve and 1.3% among treatment-experienced adults. Figure 3 shows trends in TB incidence projected for treatment-naïve and treatment-experienced adults over a 25-year period.

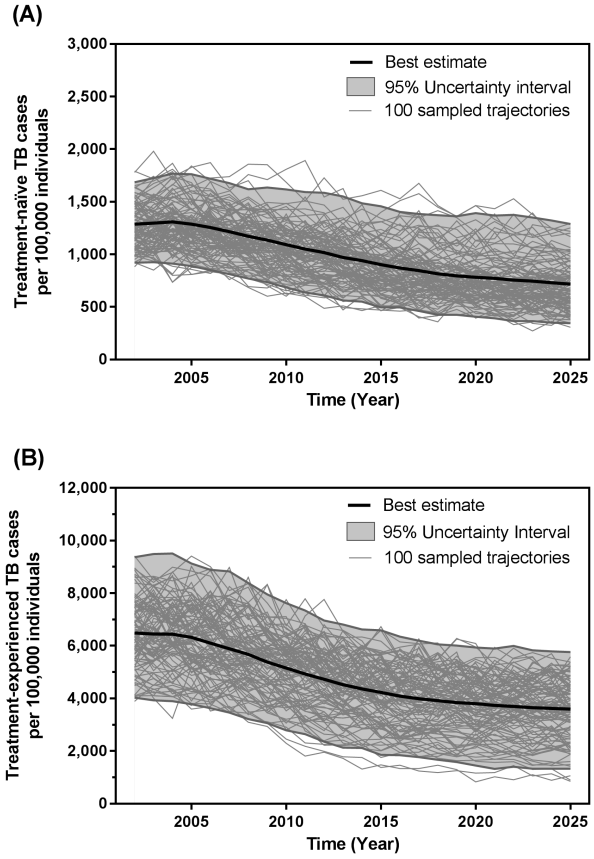

Figure 3. TB incidence among treatment-naïve (Panel A) and treatment-experienced (Panel B) adults between 2003 and 2025 projected under the baseline scenario
The best estimate of TB incidence (bold black line) represents the mean value of the sampled trajectories.

Epidemiologic impact of the interventions

We project that annual TACF among individuals who had completed TB treatment would reduce the average duration of infectious disease in this group from 10.4 months (baseline) to 5.0 months. TACF alone would avert a total of 632 (-93; 1,794) incident TB cases between 2016 and 2025, 14% (-3%; 28%) of all incident TB cases projected under the baseline scenario. Over the same time period, TACF would avert a total of 148 (-3; 427) TB deaths, 21% (0%; 41%) of all TB deaths projected under the baseline scenario.

The implementation of TACF in combination with 2°IPT would avert 1,776 (518; 3,616) incident TB cases between 2016 and 2025, 40% (20%; 59%) of all incident TB cases projected under the baseline scenario. The combined targeted intervention would avert a total of 277 (61; 686) TB deaths, 41% (16%; 62%) of all TB deaths projected under the baseline scenario.

Figure 4 shows trends in TB incidence, prevalence and mortality under the baseline scenario, under TACF alone, and under combined TACF and 2°IPT. The average annual decline in TB incidence between 2016 and 2025 relative to 2015 was 1.7% at baseline (no intervention), 3.1% under annual TACF and 5.5% under annual TACF in combination with 2°IPT.

Sensitivity analyses demonstrate that less vigorous use of TACF and 2°IPT results in reduced impact, but the flattening of the effect as probability levels of 2°IPT and periodicity of TACF increase suggests a saturation effect (Figure 5).

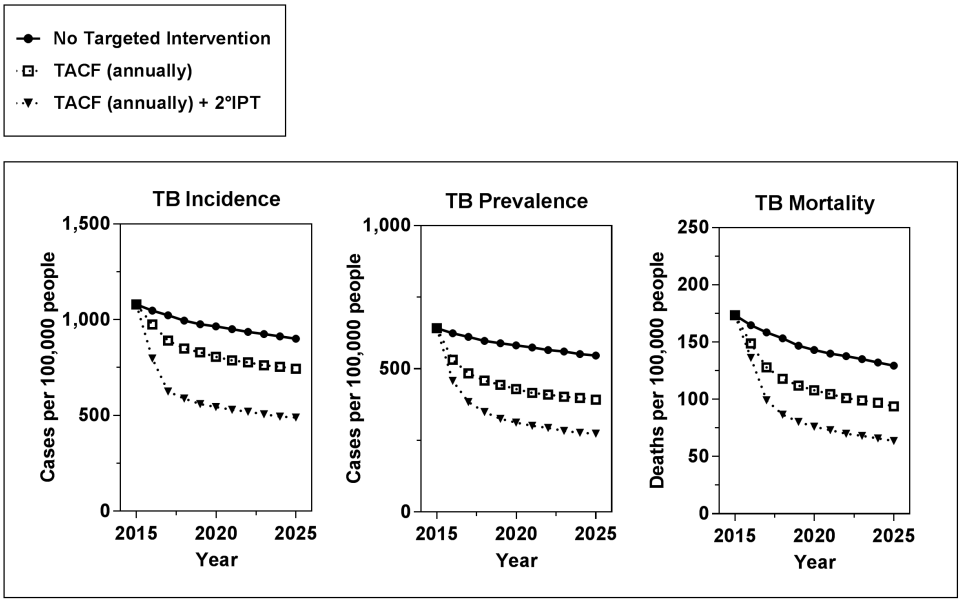

Figure 4. Best estimates of the projected epidemiologic impact of interventions targeted to individuals with a history of previous complete TB treatment in a high-incidence setting in suburban Cape Town, 2016 - 2025; comparison between the baseline scenario (no targeted intervention), annual targeted active case finding (TACF) alone, and TACF in combination with secondary isoniazid preventive therapy (2°IPT)

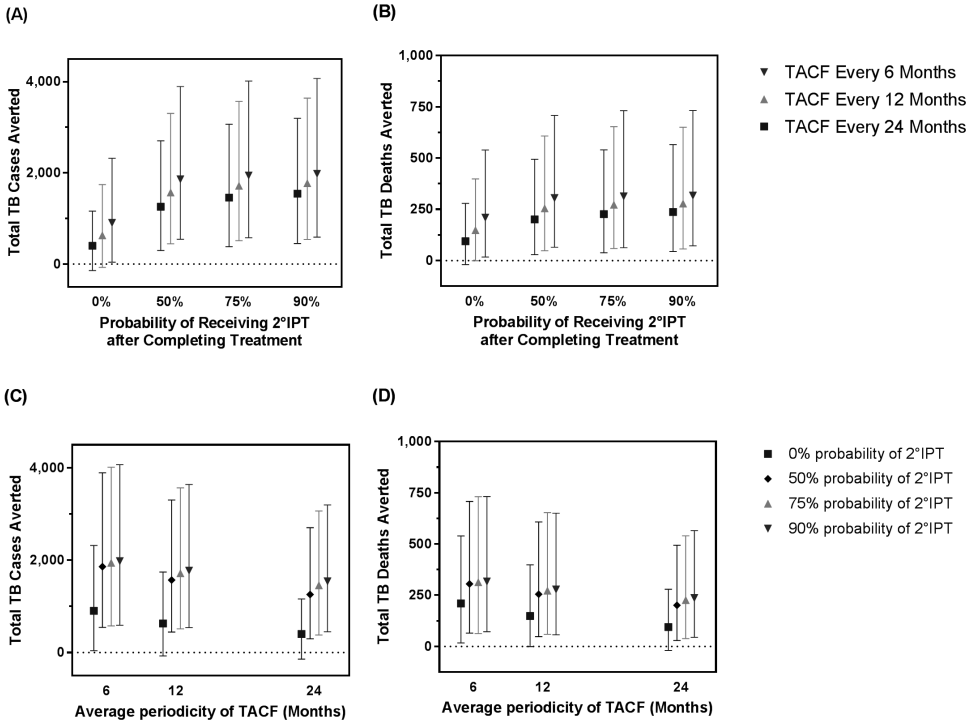

Figure 5. Sensitivity analysis of the projected impact of TACF and 2°IPT on the total number of incident TB cases (A, C) and TB deaths (B, D) averted between 2016 and 2025. Panels A and B show best estimates of the projected impact for varying probabilities of the target population being enrolled in 2°IPT plotted for different average intervals of TACF. Panels C and D show the inverse plot of TACF intervals (now x-axis) and probability of the target population being enrolled in 2°IPT (now labelled categories); 0% probability of 2°IPT equivalent to TACF only; space between data points of different series is for better readability and not proportional to scale of the x-axis; error bars represent 95% uncertainty intervals

Discussion

In this study, we used a calibrated population-based mathematical model to project the impact of two types of interventions targeted to previously treated people in a high TB prevalence setting. Our results suggest that if TACF and 2°IPT were introduced to complement existing TB control efforts, the burden of TB could be substantially reduced. Our study supports the idea that previously treated people play an important role in sustaining TB epidemics in southern Africa, and that efforts for prevention and prompt detection of recurrent TB [25] could offer novel opportunities for TB control in these settings.

We propose these targeted control interventions during a time when untargeted efforts, such as population-wide enhanced case finding and household-based screening [7] and mass isoniazid preventive therapy [8] have yielded insufficient evidence of impact, and where novel approaches are urgently needed to reduce the burden of TB in communities most affected by the disease. Targeting control efforts to groups at high risk of TB may enable health services to make more efficient use of available resources. In many high TB prevalence settings, previously treated people may be easily identified and experience an elevated risk of TB [15], therefore they may be an attractive target for focused interventions.

We project that within 10 years, a combination of TACF and 2°IPT could avert more than one-third of incident TB cases and TB deaths in our study setting. TACF alone can have considerable impact on TB prevalence and mortality and a sizable, but smaller, impact on incidence. Our projections show that much of the impact of TACF and 2°IPT accrues in the first few years following their implementation. The decreasing impact over time likely reflects a saturation effect, suggesting the opportunity to use targeted interventions as part of an adaptive control strategy [20].

Our study constitutes a first step towards better understanding the impact of interventions targeted to previously treated people in high-incidence settings. However, several limitations must be noted. We applied our model to a specific setting with a high TB incidence and where high rates of recurrent TB due to relapse and reinfection had been previously reported [11,13,26]. We note that the impact of interventions targeted at previously treated people which we project for this setting may not be easily generalized to other high-incidence settings for several reasons. High rates of recurrent TB have been reported from several other high-incidence settings [9,10,12,27]. However, the population-level impact of targeted interventions will also depend on the size of the target group and their contribution to TB transmission in the population. In this particular setting, persistently high rates of incident TB have generated a large subgroup of people who had previously been treated for TB (~10% of all adults) and who constitute a substantial fraction of the prevalent TB burden in the population (~30% of prevalent cases) [28].

While our projections are consistent with the epidemiology of TB in other high-incidence communities in South Africa [5,15], we expect interventions among previously treated people to be less impactful in settings with lower TB incidence, and where a smaller proportion of the TB burden is attributable to former TB patients. For example, previously treated people accounted for 4.1% of the adult population and for 13% of prevalent TB cases in Lusaka, Zambia [6], and for 1.5% and 15%, respectively, in Nigeria [29], two settings with lower TB incidence compared to our study setting. Nonetheless, given that new approaches for TB control are most needed in areas where TB incidence has been persistently high, our results suggest that efforts to both prevent and rapidly detect and treat recurrent disease will produce important health benefits.

Differences in the prevalence of HIV in a population might influence the impact of interventions targeted to previously treated people in several ways. Communities with higher HIV prevalence might experience more recurrent TB given the elevated risk of reinfection TB among HIV-infected individuals [30], and thus benefit more from similar interventions. Survival after a first TB episode may be reduced among those not on ART; those on ART may be

subject to more regular clinical follow-up that would limit the benefit of additional case finding interventions in this group.

The population-level impact of TACF and 2°IPT will be dependent upon existing patterns of passive health-care seeking behaviour. In settings where there are longer delays to diagnosis, additional interventions to more rapidly identify and treat recurrent cases would be more impactful, whereas in areas where individuals self-present quickly after onset of symptoms, we would expect more modest returns from investment in combined TACF and 2°IPT interventions.

Uncertainty around parameters of the natural history of TB, particularly those determining reinfection, disease progression and mortality among previously treated individuals, leads to substantial uncertainty in the modeled outcomes. To avoid bias towards higher estimates of impact, we used conservative prior ranges of parameters for treatment-experienced adults, similar to those among treatment-naïve adults. Specifically, we did not enforce higher susceptibility, lower partial immunity or higher disease progression risk among those with a history of previous TB, but did allow posterior parameter values derived from calibration to vary by treatment history. While posterior distributions of our model are consistent with treatment-experienced people being more likely to become productively reinfected than treatment-naïve people, we did not explicitly model differential risk of exposure, which may also be a mechanism driving increased risk of recurrent disease [31]. Lower boundaries of 95% uncertainty intervals for the number of TB cases and deaths averted include negative values for 12- and 24-monthly TACF alone (Figure 5). While the impact of TACF alone, especially when conducted less frequently, is expected to be weak, we note that negative projections of impact in a small number of modeled trajectories likely relate to stochasticity, reflecting uncertainty in the course of the epidemic rather than a paradoxical impact of the interventions.

Our study is further limited by uncertainty around the effect of 2°IPT on recurrent TB. Only two studies, a randomized trial [22] and a cohort study [23], have examined the effect of preventive therapy on recurrent TB. Both were limited in size and neither attempted to distinguish between relapse and reinfection. More available data from the field would improve our projections.

We used a simple mathematical model that does not enable us to explore specific intervention designs or consider many practical issues related to implementation. In particular, in our main analysis we assumed that interventions could be aggressively rolled out in these suburban settings, i.e. that individuals with previous treatment could be effectively identified, enrolled and screened for TB on average every 12 months, that 90% could be enrolled in 2°IPT upon completing treatment and 15% would drop out from 2°IPT every year. While we believe high coverage levels of the interventions may be achieved in this relatively small sub-urban setting, the impact of these interventions would clearly be lower if interventions were less vigorously applied (Figure 5) or if some individuals were not reachable by the intervention.

Our study provides impetus for further research to better understand the individual and population-level benefits of TB control interventions targeted to previously treated people. Studies and trials of the feasibility, safety, effect, and population-level impact of TACF and 2° IPT among previously treated people in high-incidence settings would be particularly useful. Other interventions aiming to prevent recurrent TB, for example secondary prevention of TB through vaccination after treatment completion, may also be an attractive option in the future. Further mathematical modeling, in which detailed costs of interventions are also included, would be useful for policy makers as they could establish whether such interventions are cost-effective and how investment in these approaches may compare with alternatives.

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Chapter 5: High burden of prevalent tuberculosis among previously treated people in Southern Africa suggests potential for targeted control interventions

Overview:

This chapter consists of a published letter to the editor. It reports the findings of an analysis of TB prevalence survey data from 24 TB high-burden communities in South Africa and Zambia that were collected as part of a large community-randomised trial. The study aimed to investigate how common a history of previous TB treatment was, whether the prevalence of TB differed by treatment history, and to what extent previously treated individuals contributed to the overall prevalent TB burden.

Publication:

Marx FM, Floyd S, Ayles H, Godfrey-Faussett P, Beyers N, Cohen T. ***High burden of prevalent tuberculosis among previously treated people in Southern Africa suggests potential for targeted control interventions.*** *The European Respiratory Journal*: official journal of the European Society for Clinical Respiratory Physiology. 2016;48(4):1227-30. doi: 10.1183/13993003.00716-2016. PubMed PMID: 27390274.

My contribution:

I conceived and designed the study with input from T. Cohen, S. Floyd and N. Beyers. I analysed the data, wrote the first manuscript draft, finalised and submitted the manuscript. The data for this study were provided by the principal investigators (H. Ayles, N. Beyers, P. Godfrey-Faussett) of the ZAMSTAR study. S. Floyd led the data management and contributed to data analysis. All authors contributed to the study design, interpretation of the results, and writing/revision of the manuscript.

High burden of prevalent tuberculosis among previously treated people in Southern Africa suggests potential for targeted control interventions

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Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

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To the Editor:

Several studies from Southern Africa report a high risk of tuberculosis (TB) among individuals who have previously been treated for the disease compared to those never before treated [1–5]. In high-burden settings, recurrent TB may affect large numbers of individuals even after successful treatment, with exogenous reinfection as an important underlying mechanism [2–4]. For example, in Cape Town, South Africa, a city with a high incidence of TB, previously treated individuals constitute one-third of the burden of notified TB [6].

The impact of recurrent disease on TB epidemics in Southern Africa is not well understood. In particular, there is limited knowledge about the extent to which previously treated people contribute to the pool of undiagnosed prevalent TB and transmission in high-burden settings. Two prevalence surveys in Zambia [7] and Zimbabwe [8] reported that previous treatment was strongly associated with prevalent TB among HIV-uninfected individuals. Ten out of 18 smear-positive TB cases detected in a prevalence survey in a South African suburban setting had a history of previous treatment [9], consistent with the hypothesis that previously treated people contribute considerably to TB prevalence and transmission in this setting.

Better quantification of prevalent TB by treatment history can inform estimates of the importance of previously treated individuals for the dynamics of TB epidemics and help determine if specific interventions targeted to this risk group could accelerate TB control. We therefore aimed to investigate, across 24 African communities, how common a history of previous treatment was, whether the prevalence of TB differed by history of previous treatment, and to what extent previously treated individuals contributed to the overall prevalent TB burden.

We analysed data from TB prevalence surveys conducted in 2010 as the primary outcome measure of the ZAMSTAR (Zambia South Africa Tuberculosis and AIDS Reduction) study, a large, community-based intervention trial in 24 high TB and HIV burden communities, 16 in

Zambia and eight in South Africa (Western Cape Province) [10, 11]. All adults aged 18 years or above who had spent the previous night in the community were eligible to participate in the surveys. Prevalent TB was ascertained through liquid (mycobacterial growth indicator tube) culture of single sputum specimens collected on the spot and confirmed as *Mycobacterium tuberculosis* by 16S ribosomal RNA gene sequencing. Further details related to the prevalence survey design have been previously published [10]. Here, we distinguished prevalent TB among adults who reported a history of previous TB treatment (treatment-experienced) from that among adults who reported no previous treatment (treatment-naïve). This analysis was approved by the ethics committee of Stellenbosch University, Stellenbosch, South Africa (ref. number N04/10/173), and the Institutional Review Boards of Partners Healthcare, Boston, MA, USA (2014P001719/BWH), and Yale University, New Haven, CT, USA (1409014625).

All but 15 of the 90,601 adults enrolled in the prevalence surveys provided information about history of previous TB treatment. Among these, 7,362 (8.1%) were treatment experienced, and this proportion varied across the 24 communities between 2.0% and 14.9%. Previous treatment was more common in the South African communities, all of which had higher estimates of TB prevalence than the Zambian communities (Figure 1a). Treatment-experienced adults were older than treatment-naïve adults (median age 38 vs. 29 years) and more often HIV positive (45.1% vs. 14.3%).

Among 64,452 adults successfully evaluated for prevalent TB, 894 (1.39%) prevalent TB cases were detected. The mean prevalence of TB (weighted for numbers of adults evaluated) in the South African communities was 2.34 (95% CI 2.17–2.52) per 100 adults overall, 3.81 (95% CI 3.25–4.47) per 100 treatment-experienced adults and 2.13 (95% CI 1.96–2.31) per 100 treatment-naïve adults. In the Zambian communities, it was 0.56 (95% CI 0.48–0.64) per 100 adults overall, 1.01 (95% CI 0.65–1.55) per 100 treatment-experienced adults and 0.53 (95% CI 0.46–0.62) per 100 treatment-naïve adults. Prevalence was higher among treatment-experienced than treatment-naïve adults across most of the communities (Figure 1b).

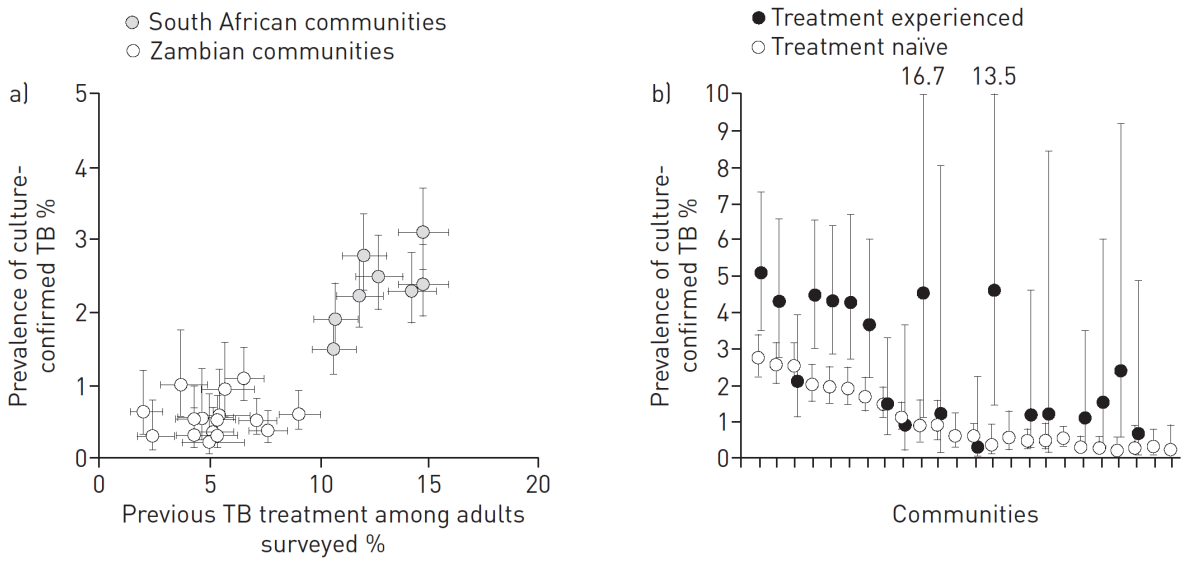

Figure 1. History of previous tuberculosis (TB) treatment and prevalent TB in 24 high TB burden communities in Zambia and the Western Cape Province of South Africa, 2010. **(a)** Correlation between the proportion of adults surveyed who reported a history of previous treatment and the prevalence of TB (regardless of treatment history). **(b)** TB prevalence among treatment-experienced and treatment-naïve adults (communities are ordered by the overall TB prevalence in the communities; no treatment-experienced cases were found in five communities). Error bars denote 95% confidence intervals.

Stratifying by HIV status suggested that the observed difference in TB prevalence was restricted to HIV-negative adults. In the HIV-negative subpopulation, TB prevalence was 3.32 (95% CI 2.57–4.27) per 100 treatment-experienced adults vs. 1.78 (95% CI 1.57–2.02) per

100 treatment-naïve adults in the South African, and 0.88 (95% CI 1.42–1.84) per 100 treatment-experienced adults vs. 0.34 (95% CI 0.27–0.42) per 100 treatment-naïve adults in the Zambian communities. Among HIV-positive adults, no significant difference by treatment history was found. TB prevalence among HIV-positive adults overall was 4.82 (95% CI 4.11–5.66) per 100 in the South African and 1.61 (95% CI 1.29–2.00) per 100 in the Zambian communities.

Among the 894 prevalent TB cases, 165 (18.5%) were previously treated. Previous treatment was also more common among these prevalent cases in the South African than in the Zambian communities (20.7% vs.10.4%), though the proportion varied considerably and exceeded 20% in nine communities. Treatment-experienced cases were more likely to be smear-microscopy positive (49.7% vs. 41.2%) and reported more current cough (43.0% vs. 34.0%) than treatment-naïve cases.

Our analysis of prevalence survey data from 24 African communities provides key insights into an important TB risk group. Individuals previously treated for TB represent a variably large fraction of the adult population, which is most sizeable in communities with the highest TB burden. Previously treated people may account for a considerable fraction of the overall prevalent TB burden and, among prevalent TB cases, those with previous treatment were more likely to be smear-positive and report active cough, suggesting substantial risk of onward transmission.

Our study is limited by its cross-sectional design, which did not enable us to establish underlying causes of recurrent TB. History of previous treatment was self-reported and no further information about the timing or outcome of previous treatment was available. Non-differential loss of specimens, attributable to a failure of positive mycobacterial controls in two laboratories, has been discussed previously but is unlikely to have introduced bias into this analysis [10]. Finally, our results probably underestimate TB prevalence in the communities because the surveys did not include individuals within healthcare facilities and other institutions.

The results of our analysis emphasise that targeted interventions to prevent [12] or early identify recurrent TB among previously treated people might be a strategy worthwhile to consider for TB control in settings with a high prevalence of TB and HIV. While ensuring adherence to and the quality of anti-TB treatment within existing control programmes remain essential priorities, such efforts may reduce relapse but will not directly prevent TB due to reinfection [2–5]. In areas where previously treated individuals are identifiable and reachable, new interventions targeted to this particular group could be practical to implement. For example, secondary preventive chemotherapy has been shown to substantially reduce the risk of recurrent TB [13, 14]. Active case finding [15] targeted to previously treated people may reduce morbidity and transmission, as it may shorten the time that recurrent disease remains undiagnosed. While such targeted interventions are beneficial to individuals at high risk of recurrence, our results suggest that their benefits may extend to the community in settings where recurrent TB contributes to transmission. Future research in which the costs of such targeted interventions, and their effects on reducing recurrent TB and associated transmission are better quantified are needed to understand if they can be a cost-effective element of improved strategies to control TB in high-burden settings.

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Chapter 6: Variation in the notified burden of previously treated tuberculosis in the 52 health districts in South Africa

Overview:

This chapter consists of an unpublished manuscript. It reports findings from an ecological analysis that was conducted using electronic TB register data from the 52 South African health districts. The aim of this study was to describe the proportion of previously treated individuals among diagnosed TB patients in the 52 health districts of South Africa. It further aimed at investigating whether this proportion varied with (1) the TB case-notification rate (2) the HIV prevalence and (3) outcomes of TB treatment among new TB patients in the districts. We discuss in this manuscript why high proportions of previously treated TB have important implications for TB control in countries and settings with a high disease burden.

My co-authors:

Ted Cohen, Pren Naidoo, Nulda Beyers

My contribution:

I conceived and designed the study with input from N. Beyers and P. Naidoo. I analysed the data, wrote the first manuscript draft and finalised the manuscript. P. Naidoo obtained permission to use the data as part of a larger underlying study. All authors contributed to the interpretation of the results and writing/revision of the manuscript.

Variation in the notified burden of previously treated tuberculosis in the 52 health districts in South Africa

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(Unpublished manuscript)

Abstract

Background. Management of tuberculosis (TB) in patients with a history of previous TB treatment poses considerable challenges to TB control due to the risk of more extensive and of drug-resistant disease, and more unfavourable treatment outcomes. We aimed to investigate the proportion of individuals previously treated for TB among routinely registered TB patients in South Africa, and whether this proportion varied across the 52 health districts.

Methods. We used data extracted from the national electronic TB register (ETR.net). An ecological analysis was conducted on all bacteriologically-confirmed TB patients treated for presumed drug-sensitive (DS-) TB in 2011, using district as unit of observation. The proportion (percentage) of previously treated TB patients was estimated using patient category information (new vs. re-treatment).

Results. A total of 182,455 bacteriologically confirmed TB patients started DS-TB treatment in South Africa in 2011 of whom 35,633 (20%) had previously been treated for TB. At the district level, the proportion of previously treated TB patients varied between 7.6% and 40% (median: 17%; IQR: 12% - 22%) and exceeded 20% in 17 of the 52 districts. We found a linear correlation between the proportion of previously treated TB patients and each of the following, the TB case notification rate per 100,000 population (Spearman correlation coefficient [r]=0.75, the HIV prevalence (r=-0.70 [inverse correlation]; P<0.001), the percentage of death during TB treatment (r=-0.29 [inverse correlation]; P=0.035) and the percentage of loss to follow-up from TB treatment (r=0.59; P<0.001).

Conclusions. There is substantial variation in the proportion of TB patients with a history of previous TB treatment across the South African health districts. The reasons for this variation and its implications for TB control programs, including the associated drug-resistant TB burden, are currently not known. We speculate that TB recurrence due to reinfection (in districts with high TB rates) and higher probability of survival following a first TB episode in the absence of HIV infection may partly explain the very high proportions of previously treated patients observed in several districts.

INTRODUCTION

Tuberculosis (TB) patients with a history of previous TB treatment represent a diverse group that is composed of individuals after successful treatment, those who were lost to follow-up or in whom treatment had failed, and those with unknown previous treatment outcome. Their management may pose considerable challenges to TB control programs. Previously treated TB is more challenging to diagnose than new TB, given the lower specificity of radiography [1] and of rapid molecular diagnostic assays [2-4], and more often presents as drug-resistant TB [5]; treatment outcomes are usually less favourable compared to first episodes of TB [6,7].

The extent to which previously treated people contribute to the overall number of TB patients varies considerably among countries worldwide. In 2015, previously treated individuals represented between 1.5% and 35% of notified TB cases in the 30 TB high-burden countries defined by the World Health Organization [8]. Highest proportions, 30% and more, are usually found in countries with a high burden of multidrug-resistant (MDR-) TB [9].

An unexpectedly high proportion of previously treated individuals (~30% over several years [10,11]) has been observed among TB patients in Cape Town, a South African metropole with a high TB incidence. Reports of high local rates of reinfection TB after previous successful TB treatment [12-14], particularly among HIV-infected individuals [10], and a majority of previously treated patients (~75% [10]) with a history of successful treatment suggest that poor treatment outcomes alone may not sufficiently explain this observation. The substantial contribution of previously treated individuals to the number of TB patients overall in Cape Town is in contrast to lower proportions reported for South Africa as a whole (7.8% previously treated TB in 2015 [8]) and other areas in the country [15-17], suggesting considerable variation at sub-country level.

Here we describe the proportion of previously treated people among diagnosed TB patients in the 52 health districts of South Africa. We aimed to investigate whether this proportion varied with (1) the TB case notification rate (2) the HIV prevalence and (3) outcomes of TB treatment in the districts. We discuss why high proportions of previously treated TB have important implications for TB control in countries and settings with a high disease burden.

METHODS

Study setting

South Africa has a population of 56.5 million people [18] and consists of nine provinces which are subdivided into 52 (health) districts. It is one of the countries with the highest burden of HIV and TB in the world. In 2015, an estimated 7.0 million (13%) people were living with HIV [19], and an estimated 454,000 people developed TB (57% HIV-co-infected), equivalent to 834 per 100,000 of the population [20].

Data sources

Data for TB patients treated in 2011 in South Africa were extracted from the national electronic TB register (ETR.net) [21]. The register was introduced by the National TB Program in 2003 and is intended to keep record of all TB patients treated for presumed drug-susceptible TB in the country. (TB patients treated for drug-resistant TB are kept in a separate register.) ETR.net includes case-based routinely collected information (including individual demographic, TB case-category, diagnostic and treatment outcome data) that was originally collected in health-care facilities throughout the country and recorded in paper-based TB treatment registers. These are collated at the sub-district or district level and transcribed into ETR.net. Data for this study came from a subset of ETR.net data that had been developed for an underlying larger evaluation of the epidemiologic situation of TB in South Africa. The data had been validated and cleaned; duplicate entries of TB patients and those of TB patients kept in the register despite pre-treatment confirmation of drug-resistant TB had been removed.

To estimate TB rates in the districts, we used published mid-year estimates of the South African population for the year 2011 [22]. Finally, we used published estimates of (district-level) HIV prevalence in 2011 derived from the National Antenatal Sentinel HIV prevalence survey [23].

Study definitions

Definitions used in this study are in accordance with standard definitions of TB recording and reporting in South Africa [24]. The term ‘bacteriologically-confirmed TB’ is reserved for TB patients for whom *M.tb* was confirmed in a clinical specimen either by smear-microscopy, culture of Xpert MTB RIF. History of previous TB treatment in our study was ascertained by

recorded patient categories. The category 'New TB' is used for patients without known history of prior TB treatment. Previously treated TB patients, include those in the category Relapse (re-treatment after previous treatment success) as well as those in the categories 'Re-treatment after failure', 'Re-treatment after loss to follow-up' and 'Other re-treatment'. In accordance with international reporting, we refer to the latter three categories as previously treated -non-relapse- TB patients. Definitions of explanatory variables used in this study are shown in Table 1.

Study design

We conducted an ecological analysis at the level of the 52 South African health districts. The study population included all bacteriologically-confirmed TB patients (adults, children, all forms of TB) who started treatment for presumed drug-susceptible TB in South Africa in 2011. The outcome measure (dependent variable) was the proportion of individuals with a history of previous TB treatment among all bacteriologically-confirmed TB patients, expressed as a percentage. We investigated associations between the outcome variable and the following explanatory variables (see also Table 1):

General-population:

- TB case notification rate: new and relapse* TB cases per 100,000 population
- HIV prevalence (%)

New TB patients:

- HIV-co-infection (%)
- Median CD4 count (among HIV co-infected)
- Treatment success (%)
- Death during TB treatment (%)
- Loss to follow-up during TB treatment (%)

Table 1. Overview of district-level indicators and data sources used

Indicator	Definition	Data source
TB case notification rate	New and relapse TB patients per 100,000 population	ETR.net database / 2011 South Africa population census
HIV prevalence (%)	Estimated percentage of the population living with HIV infection	South African Antenatal Sentinel HIV prevalence survey 2011
HIV co-infection (%)	Percentage of new TB patients with documented positive HIV status; HIV status is usually recorded on the basis of either a positive HIV test conducted at the beginning of TB treatment or positive HIV status self-reported by the patient.	ETR.net database
CD4 count (HIV-positive)	Median CD4 count (CD 4 cells per mm^3 serum) among HIV-positive new TB patients with documented CD4 count result; CD4 count is routinely ascertained and documented after a TB patient tests positive for HIV at the beginning of TB treatment.	ETR.net database
Treatment success (%)	Percentage of new TB patients who were bacteriologically cured and those who completed their treatment and were considered successfully treated (but without bacteriological confirmation of cure)	ETR.net database
Death during treatment (%)	Percentage of new TB patients who died during TB treatment	ETR.net database
Loss to follow-up from treatment (%)	Percentage of new TB patients who were lost to follow-up during TB treatment (i.e. those who interrupted their treatment for at least two consecutive months)	ETR.net database

* In line with WHO standards for recording and reporting, the TB case-notification rate does not include previously treated TB cases other than relapse who might have a re-treatment episode after previous loss-to follow-up, after treatment failure or after transfer out.

Data Analysis

We used STATA™ 14.2 statistical application (Stata Corp, College Station, TX, USA) for data analysis. Our analysis comprises descriptive statistics of the absolute number and proportion (percentage) of previously treated individuals among bacteriologically-confirmed TB patients, and of the categories of previously treated patients (relapse vs. non-relapse).

We investigated district-level correlation between the proportion of previously treated people (outcome measure) and each of the explanatory variables. Spearman correlation coefficients (r) and their two-tailed significance were estimated. To investigate independent associations, we also included all explanatory variables in a generalised linear model with a logit link of the binomial family [25]. This type of linear model takes into account that the dependent variable, the proportion previously treated TB, is confined between 0 and 1 (0% and 100%).

We also conducted secondary analysis. Here we recalculated all study measures and repeated the analysis after including all TB patients, i.e. also those who were clinically diagnosed or for whom bacteriological results were not documented in the TB register.

Ethics Statement

This sub-study is part of a larger study that was approved by the Ethics Committee of the Faculty of Medicine and Health Sciences of Stellenbosch University (Reference # N16/07/088). The South African National Department of Health who is the custodian of the ETR data gave consent to use the data for this study and to publish its results.

RESULTS

Overview of the study population

In 2011, a total of 182,455 bacteriologically-confirmed TB patients started TB treatment for (presumed) drug-susceptible TB in South Africa, of whom 35,633 (20%) had previously been treated for TB. The majority of previously treated patients were relapse patients (re-treatment after treatment success; 59%). Bacteriologically-confirmed TB patients represented 46% of all TB patients diagnosed and included few children and few extra-pulmonary TB patients. Table 2 summarises key characteristics of the study population.

Table 2. Overview of TB patients in South Africa who started treatment for (presumed) drug-susceptible TB in 2011

Variable	Category	Bacteriologically-confirmed*				Total	
		Yes		No			
		N	*Col%*	*N*	*Col%*	*N*	*Col%*
Total		182,455	-	216,943	-	399,398	-
Patient category	New	146,822	80.5	186,606	86.0	333,428	83.5
	Previously treated, relapse	21,084	11.6	8,038	3.7	29,122	7.3
	Previously treated, non-relapse	14,549	8.0	22,299	10.3	36,848	9.2
Sex	Female	81,372	44.6	104,319	48.1	185,691	46.5
	Male	101,083	55.4	112,624	51.9	213,707	53.5
Age	0-14 years	4,121	2.3	45,145	20.8	49,266	12.3
	15+ years	178,334	97.7	171,798	79.2	350,132	87.7
Site of TB disease	Extrapulmonary	1,828	1.0	50,360	23.2	52,188	13.1
	Pulmonary	180,627	99.0	166,583	76.8	347,210	86.9
HIV status information	Not documented	27,806	15.2	45,626	21.0	73,432	18.4
	Documented	154,649	84.8	171,317	79.0	325,966	81.6
HIV status (among documented)	Negative	59,758	38.6	53,122	31.0	112,880	34.6
	Positive	94,891	61.4	118,195	69.0	213,086	65.4
CD4 count (among HIV-positive)	Not documented	23,346	24.6	41,793	35.4	65,139	30.6
	Documented	71,545	75.4	76,402	64.6	147,947	69.4

* Bacteriological confirmation (by any method) documented in the treatment register

Previous TB treatment among bacteriologically-confirmed TB patients in the 52 South African health districts

The total number of bacteriologically-confirmed TB patients in each of the 52 districts ranged from 425 to 17,745 (median: 2,726; interquartile-range [IQR]: 1,719 - 3,696).

The proportion of previously treated individuals among these TB patients varied among the districts between 7.6% and 40% (median: 17%; IQR: 12% - 22%) and exceeded 20% in 17 of the 52 districts (Figure 1). The median percentage of relapse patients among patients with a history of previous TB treatment was 61% (IQR: 50% - 70%). Relapse was more common than non-relapse especially in districts with a high proportion of previously treated TB patients overall (Figure 2).

We found a strong correlation between the TB case notification rate and the proportion of previously treated TB patients (Spearman's correlation coefficient r=0.75; P<0.001; Figure 3a). Estimates of HIV prevalence in the districts correlated inversely with the proportion of previously treated TB patients (r=-0.45; P<0.001; Figure 3b).

We also found a strong inverse correlation between the percentage of new TB patients with documented HIV co-infection and the proportion of previously treated TB patients in the districts (r=-0.70; P<0.001; Figure 4a). Furthermore, the median CD4 cell count among HIV-positive new TB patients correlated with the proportion of previously treated TB patients (regardless of HIV status) in the districts (r=0.52; P<0.001; Figure 4b).

There was no correlation between the percentage of treatment success among new TB patients and the proportion of previously treated TB patients (r=-0.02; P=0.842). However, both death during TB treatment (r=-0.29 [inverse correlation]; P=0.035; Figure 4c) and loss to follow-up from TB treatment (r=0.59; P<0.001; Figure 4d) correlated with the proportion of previously treated TB.

At multivariable analysis, the TB case notification rate (P<0.001), HIV co-infection among new TB patients (P=0.001) and the percentage of death during TB treatment (P=0.042) remained associated with the proportion of previously treated TB among bacteriologically-confirmed TB patients (Table 3). The multivariable model explained 81% of the variation in the observed proportions of previously treated TB in the districts.

Including TB patients without documented bacteriological confirmation in the analysis did not noticeably change the observed associations.

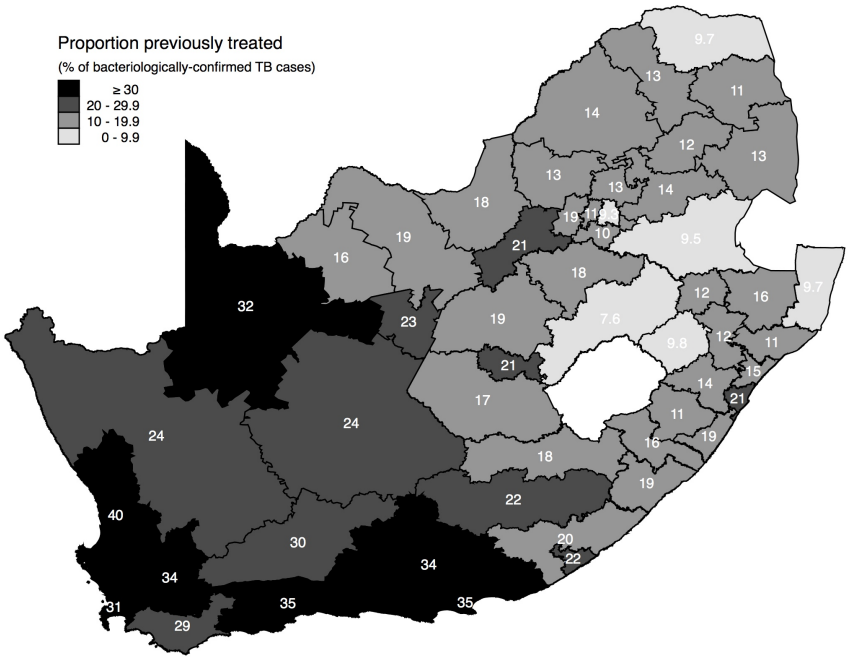

Figure 1. Previously treated patients as a percentage of all bacteriologically-confirmed TB patients in 52 South African districts, 2011

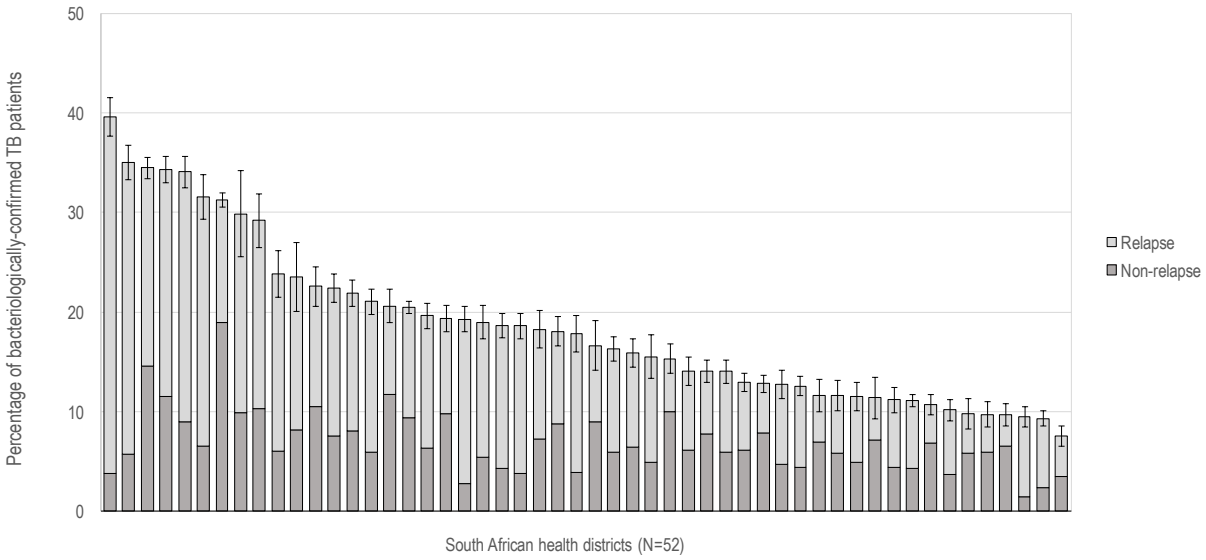

Figure 2. Relapse and other previously treated (non-relapse) patients as a percentage of all bacteriologically-confirmed TB patients in 52 South-African districts, 2011. Error bars denote 95% confidence intervals of the percentage of previously treated patients

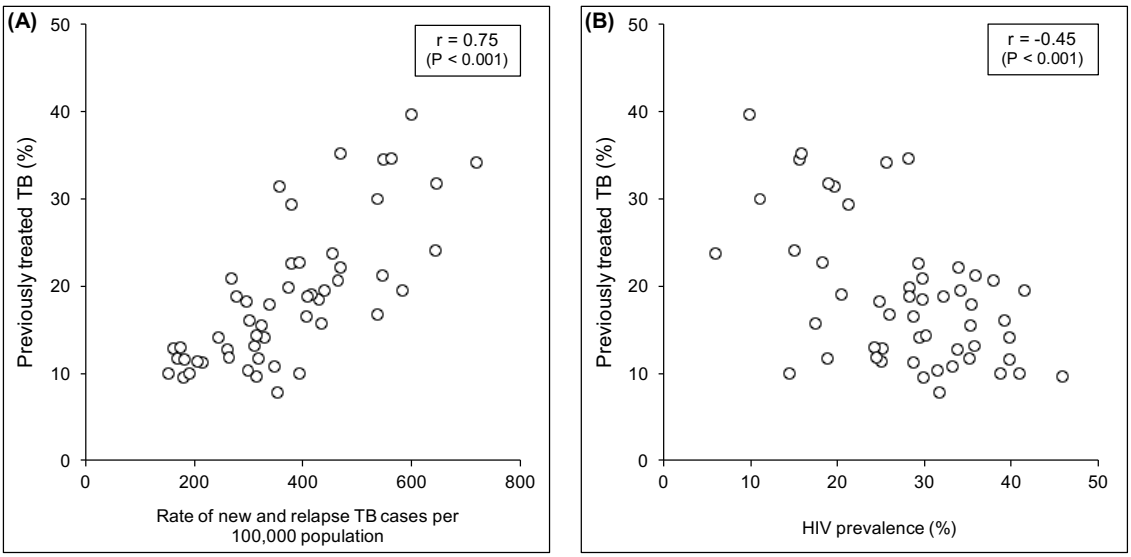

Figure 3. Correlation between the percentage of previously treated TB among bacteriologically-confirmed TB patients, the background rate of TB (left) and population-level HIV prevalence (right) in 52 South African districts, 2011; upper-right boxes in each of the graphs show Spearman's correlation coefficient (r) and two-tailed test of independency (P-value)

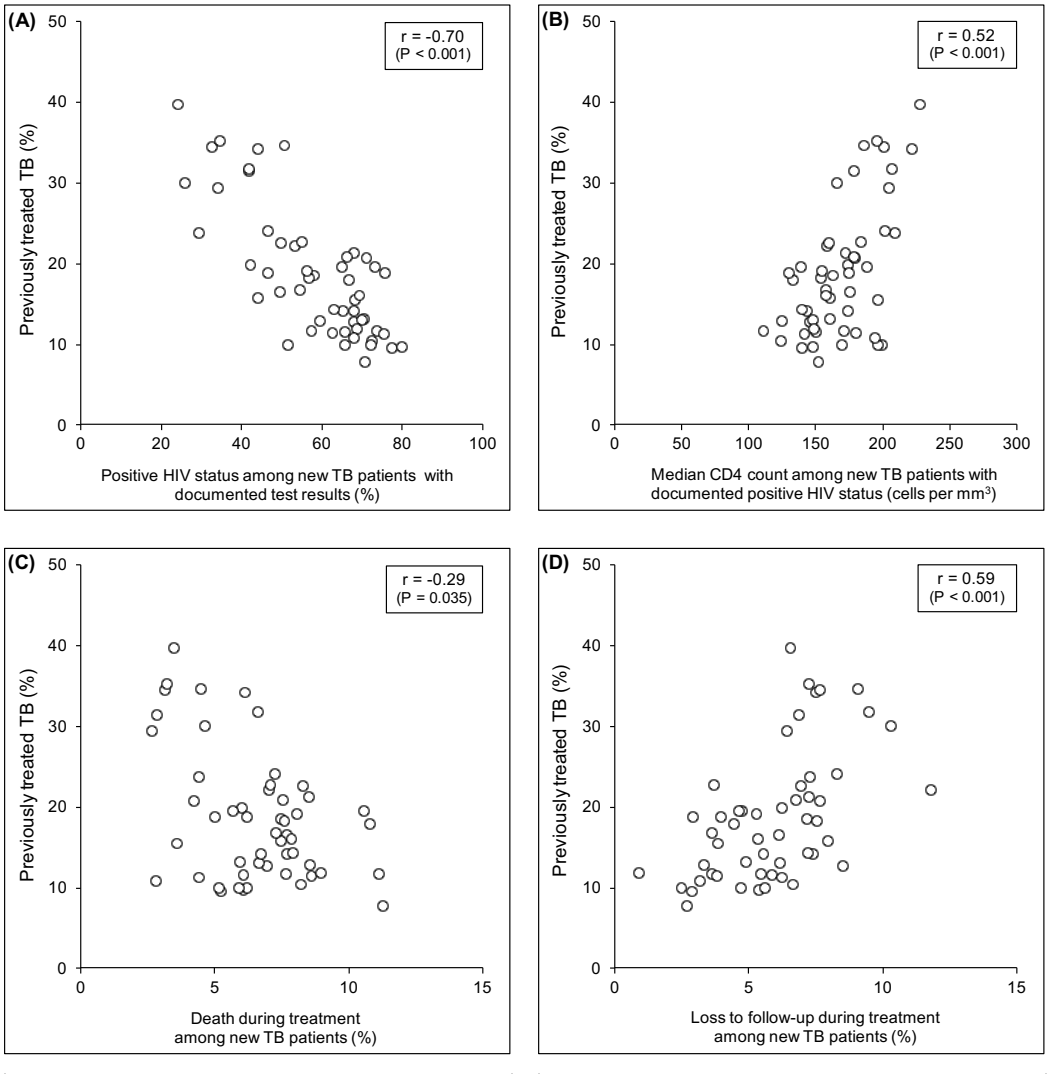

Figure 4. Correlation between the percentage of previously treated TB and characteristics of bacteriologically-confirmed *new* TB patients in 52 South African districts, 2011; upper-right boxes in each of the graphs show Spearman's correlation coefficient (r) and two-tailed test of independency (P-value)

Table 3. Generalised linear regression model of the proportion of previously treated TB* in the 52 South African health districts, 2011

		UNIVARIABLE			MULTIVARIABLE		
Reference	**Variable**	**Odds ratio**	**95% confidence interval**	**P-value**	**Odds ratio**	**95% confidence interval**	**P-value**
Total population	Rate of new & relapse TB cases (per 1,000)	1.028	(1.022-1.034)	<0.001	1.018	(1.011-1.025)	<0.001
	HIV prevalence (%)	0.969	(0.957-0.982)	<0.001	1.003	(0.990-0.016)	0.672
New TB cases	HIV co-infection (%)	0.973	(0.968-0.978)	<0.001	0.984	(0.975-0.993)	0.001
	CD4 count, HIV-positive (median)	1.012	(1.008-1.016)	<0.001	0.999	(0.994-1.004)	0.652
	Treatment success (%)	1.005	(0.983-1.027)	0.670			
	Death during treatment (%)	0.890	(0.837-0.951)	<0.001	0.954	(0.911-0.998)	0.042
	Loss to follow-up from treatment (%)	1.146	(1.088-1.207)	<0.001	1.024	(0.984-1.066)	0.247

* Modeled as a fraction of all bacteriologically-confirmed TB cases (ranging between 0 and 1)

DISCUSSION

We show that the proportion of previously treated TB patients varies considerably at sub-country level in South Africa, ranging from less than 10% to 40% of bacteriologically-confirmed TB patients in the districts. TB patients classified as relapse (i.e. those with a history of TB treatment success) account for the vast majority of previously treated patients in most districts of South Africa.

The reasons for the very high proportions of previously treated TB patients in several districts are currently not known. They may reflect the true contribution of previously treated people to the overall TB burden in the districts. This hypothesis is supported by (2010) TB prevalence survey data from eight communities in the Western Cape Province which showed that previously treated adults represented a relatively large subgroup (10-15%) of the adult population [26]. This subgroup had a high prevalence of bacteriologically-confirmed TB (median: 4.3%) and represented a large proportion of the overall prevalent TB burden (median: 22%) [26].

Our study provides insights into factors determining variation in the proportion of previously treated TB patients in the districts. We found a positive relationship between the proportion of previously treated TB and the TB case notification rate per 100,000 population. The rate of treated TB patients determines the relative size of the subgroup of people with a history of previous TB treatment. The larger this subgroup in the population, the larger the proportion of overall TB cases that may arise from it. We speculate that TB case notification rates in the districts may also reflect local TB incidence rates which correlate with the contribution of reinfection to TB among previously treated people [27,28]. Molecular studies in settings with a very high TB incidence have shown that the rate of reinfection TB after successful TB treatment may exceed several-fold the rate of new TB [13,14,29] and suggest individual heterogeneity in the risk of becoming infected or in progressing to TB disease upon infection [29].

We found an inverse relationship between the proportion of previously treated TB and the prevalence of HIV infection in the districts. In districts with high HIV prevalence, a large proportion of the population is highly susceptible to TB (due to HIV infection), probably regardless of previous TB treatment. Furthermore, HIV-infected people with a first episode of TB most likely represent a group of people with more advanced immunosuppression compared to those who did not develop TB and may thus experience a higher mortality risk. We speculate that this differential degree of immunosuppression and associated mortality among people living with HIV contributes to the lower proportions of previously treated people in districts of high HIV prevalence, consistent with our finding that the degree of immunosuppression (as measured by median CD4 counts) among HIV-infected new TB patients correlated positively with the proportion of previously treated TB.

Our findings suggest that unfavourable outcomes of TB treatment contribute at least partially to the burden of previously treated TB in the districts. As expected, the percentage of death during first-time treatment correlated inversely with the proportion of previously treated TB. We found evidence for a correlation between the percentage of loss to follow-up among new TB patients and the proportion of previously treated TB in the districts, consistent with high rates of TB reactivation [13] and re-treatment after previous loss to follow-up reported earlier [13,30]. However, the fact that the vast majority of TB patients were classified as relapse (previous treatment success) indicates that loss to follow-up from TB treatment might not sufficiently explain the high proportions of previously treated TB patients observed in some of the districts.

Our study has limitations. It is based on routinely collected and recorded TB program data that may be incomplete and inaccurate. History of previous TB treatment among TB patients is usually self-reported; under-reporting of treatment history is likely [31] and may have contributed to the observed variation of previously treated TB observed in the districts. Under-recording of treatment status may be an issue especially in more recent years after the

suspension of the ("Category II") re-treatment regimen (2014) [24]. Incomplete and inaccurate information may also have affected the inclusion of bacteriologically-confirmed TB patients in our analysis as well as measures of district-level variables used in this study such as the prevalence of HIV infection or TB treatment outcomes.

This was an ecological analysis of indicators crudely measured at the level of the South African health districts and precludes causal inference about the mechanisms and individual risk factors of TB among previously treated people. Our analysis is explorative; residual confounding of other population-level factors is possible. Furthermore, the data used were obtained for a single year and thus do not allow to describe and investigate temporal relationships. For example, associations between district-level treatment outcomes and the proportion of previously treated TB patients need to be interpreted with caution because they were estimated for the same year and do not take variation in prior years into consideration. However, we do not believe that more complex analysis over several years would have affected our findings.

We were unable to directly estimate case notification rates stratified by treatment history because the number of people with previous TB treatment in the general population was not known. The study is based on TB patients who were diagnosed and treated in the districts, and we had no information about the extent to which differential health-care seeking behaviour and treatment initiation upon positive TB diagnosis contributed to variation in the proportion of previously treated TB in the districts.

We were unable to investigate the potential relationship between the coverage/introduction of ART among HIV-infected TB patients. While ART reduces the risk of recurrent TB [32], it is also expected to increases survival among TB patients [33]. It is thus not clear whether expansion of ART will lead to increased survival and more previously treated TB or reduce previously treated TB due to immune-reconstitution.

Finally, our study was based on TB patients treated for presumed drug-susceptible TB. We were thus unable to investigate whether the prevalence of drug-resistant TB was associated with the proportion of previously treated TB patients in the districts. Previous TB treatment is a known risk factor for drug-resistant TB [34], and vice versa, patients with drug-resistant TB are also known to be at higher risk of recurrent TB [35]. Globally, highest proportions of previously treated TB patients are usually reported from countries with a high burden of MDR-TB [9]. However, the role of drug-resistance as a cause or consequence for previously treated TB in the South African districts is currently not known.

CONCLUSIONS

Our findings have implications for TB control. We show that findings of very high proportions of previously treated TB in Cape Town extend to several other South African districts. TB control programs in these districts are likely to face the specific challenges of diagnosing and treating TB among previously treated people. For example, South Africa has meanwhile implemented Xpert MTB/RIF countrywide as a primary diagnostic tool replacing smear microscopy (notably in the time after data for this study were recorded). In districts where previous TB treatment is common, the known high false-positivity rate of Xpert MTB/RIF among previously treated presumptive TB cases [4] might lead to substantial over-diagnosis. Furthermore, repeated exposure to TB drugs is known as a key risk factor for the acquisition of drug-resistance [34]. Whether drug-resistant TB is more likely to emerge in districts with a high proportion of previously treated TB is currently not known. High rates of unfavourable treatment outcomes [6,7], in particular loss to follow-up [7], associated with a history of previous TB treatment may affect the performance of treatment outcomes overall in these districts.

High proportions of previously treated TB patients in several districts, especially of patients with a history of successful TB treatment, raise questions about the performance of TB

treatment. Intermittent [36] and irregular [37] TB treatment as well as (undetected) drug resistance [37] have been identified as important risk factors of recurrent disease after treatment completion. Understanding how the performance of TB control programs relates to the high burden of previously treated TB in the districts will therefore be crucial.

Targeting additional TB control measures toward previously treated people may be an attractive strategy to reduce transmission, morbidity and mortality of TB in settings where previously treated individuals contribute substantially to the local TB burden [26]. A recent mathematical model of TB in suburban Cape Town projected that the roll out of targeted active case finding and secondary preventive therapy after successful TB treatment could produce considerable population level benefits (Chapter 3). Whether and under what conditions such targeted TB control strategies are feasible to implement and cost-effective for TB control in different areas of South Africa remains to be determined.

Our analysis supports previous evidence that previously treated people constitute an important TB high-risk group in South Africa. Increased efforts are warranted to address the specific needs of this group, to prevent TB and the adverse health and socio-economic consequences that the disease continues to cause them and their families.

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Chapter 7: Discussion

7.1. Overview

The research presented in this dissertation focused on TB epidemiology and control in high-incidence settings and comprises a total of 5 studies. Its overall aim was to characterise the risk of TB among people with a history of previous TB treatment and to project the impact of control interventions targeted at this subgroup on the trajectory of TB epidemics in high-incidence settings. The 5 studies used different datasets, settings and methodologies, but all focused on the same aim.

The first three studies referred to a TB high-incidence setting in suburban Cape Town. Using routine TB programme data, I estimated the rate of TB among previously treated people and investigated whether this rate differed by whether they had completed their previous TB treatment episode or not (Chapter 2). On the basis of routine data and paired strain-type DNA fingerprinting results from diagnostic samples collected for a subset of 130 TB patients, I investigated the temporal dynamics of relapse and reinfection TB after successful completion of TB treatment (Chapter 3). I then used a transmission-dynamic mathematical model calibrated to data from the same high-incidence setting to project the population-level impact of two TB control interventions, targeted active case finding (TACF) and secondary preventive therapy (2°IPT) among people who had successfully completed their TB treatment (Chapter 4). The two final studies used data from other high-incidence settings to investigate key epidemiological characteristics that may help to determine whether projections from our mathematical model may be relevant to other high-incidence settings in Southern Africa. I investigated the extent to which previously treated people contribute to the prevalent TB burden in 24 communities in South Africa and Zambia (Chapter 5), and the (detected) incident TB burden in the 52 South African health districts (Chapter 6).

In this chapter, I briefly summarise the key findings of the various studies (chapters) of this dissertation in the context of the literature (7.2 - 7.4), and I discuss conclusions along with strengths and limitations of each study. This is followed by strengths and limitations of the dissertation as a whole (7.5) and a summary of the evidence gained and its relevance, with a particular focus on improving TB control in high-incidence settings (7.6). The chapter closes with recommendations for future research (7.7).

7.2. TB among previously treated people – findings from a TB high-incidence setting in suburban Cape Town

Setting

Before discussing key findings from the first two studies (Chapters 2 and 3), the characteristics of the study setting need to be revisited. The setting consists of two well-characterised adjacent suburban communities of approximately 39,000 residents in suburban Cape Town, a South African city with a known high burden of TB and HIV. Two primary health-care clinics serve the local population and provide supervised TB treatment. Facility-based treatment register data are used for recording and reporting of TB cases and for monitoring of treatment outcomes according to international standards.

In 2013, the two TB clinics notified a total of 416 TB cases (adults and children, all forms of TB) of whom 133 (32%) were recorded as previously treated cases. All but 4 TB cases had their HIV status documented, and 21% of TB patients were documented HIV-positive (new: 16%; previously treated: 30%). Of the 416 TB cases treated in 2013, 340 (82%) successfully completed their treatment, and 40 (9.6%) were lost to follow-up during TB treatment.

Molecular and spatial epidemiology studies suggest high ongoing community transmission of *M.tb* [1, 2]. Persistently high annual risks of infection (estimated 3.7% in 1999 and 4.1% in 2005 [3]) suggested that conventional TB control, while improving individual outcomes, fails to reduce transmission in this setting [2].

Data from a lung health survey suggest that a large proportion (~10%) of the local adult population has a history of previous TB treatment [4]. Two earlier studies reported high rates of recurrent TB among people with a history of successful TB treatment. Both studies had used DNA fingerprinting to distinguish whether recurrence after previous successful TB treatment was due to endogenous reactivation (relapse) or exogenous reinfection and both had concluded that exogenous reinfection is a major contributor to recurrent TB in the communities [5, 6].

In this context, we conducted two large retrospective cohort studies using routine TB programme data to investigate rates of TB after complete and incomplete treatment and the dynamics of relapse and reinfection TB over a longer over a longer time period and on a larger number of TB patients. The study population consisted of all smear-positive TB patients diagnosed and treated between 1996 and 2008.

Key findings in the context of the existing literature

The first study (Chapter 2) was based on all smear-positive TB patients who had either successfully completed treatment or were lost to follow-up during TB treatment in these two communities. We found that, of 2,136 smear-positive TB patients in total, 291 (13.6%) were subsequently re-treated for smear-positive TB after a median time of 17 months since the end of the initial treatment episode. The overall rate of re-treatment for smear-positive TB was 2.68 (95%CI: 2.39-3.01) per 100 person-years (PYRS).

As expected, this rate differed according to whether individuals had completed their initial TB treatment. It was highest after loss to follow-up, 6.86 (5.59 - 8.41) per 100 PYRS. Adjusted analysis showed that the rate after loss to follow-up was nearly 4-times higher than that after cure (adjusted hazard-ratio: 3.97 [3.00 - 5.26]; P<0.001). By the end of the second year, 28% (23% - 34%) of TB patients who were lost to follow-up had been diagnosed again with smear-positive TB. Of the 92 individuals re-treated for smear-positive TB after previous loss to follow-up, 34 (37%) were lost to follow-up again during their re-treatment episode.

Individuals after loss to follow-up represented 32% of all individuals with smear-positive TB re-treatment.

The rate of re-treatment for smear-positive TB among individuals who had successfully completed their initial TB treatment was 2.09 (1.81 - 2.41) per 100 PYRS after cure, and 2.19 (1.29 - 3.69) per 100 PYRS after treatment completion (i.e. without bacteriological evidence of cure). These rates were consistent with an estimate documented by Verver et al. from the same study setting (2.7 per 100 PYRS after treatment success) [6]. Their study was based on a smaller sample of patients and had included culture-positive/smear-negative recurrences, whereas we based the outcome recurrent TB solely on the diagnosis of smear-positive TB because culture was not routinely conducted for all patients in the study period.

The rate of recurrent after successful treatment found in our study compares well with the estimate from a population cohort in Northern Malawi (2.4 recurrences per 100 PYRS) [7], but was lower than rates estimated in Uganda (8.4 per 100 PYRS), Zambia (6 per 100 PYRS among HIV-negative individuals) [8] and among gold miners in Gauteng Province, South Africa (10.3 per 100 PYRS) [9]. While our study and that by Verver et al. [6] were based on passive follow-up, many of these other studies employed active follow-up as a means to detect recurrent TB after treatment success and thus were able to detect recurrences independently of individuals accessing health-care [8-10], or they had been conducted among populations that were routinely under more rigorous health observation (e.g. studies conducted in mining populations) [11, 12]. Differences in recurrence rates may also be explained by the prevalence of HIV co-infection, which relatively low (<15%) in our setting (see also limitations).

The rate of recurrent TB after cure in our setting (2.09 per 100 PYRS) also needs to be interpreted in relation to the rate of new TB in the setting. During the study period, less than 0.5 new smear-positive TB patients per 100 residents had been observed per year [3], suggesting that successfully treated patients in the communities were at least 4-times more likely to be detected with smear-positive TB compared to people without a history of previous TB treatment.

To investigate whether recurrent TB was due to relapse and reinfection, we conducted a retrospective cohort study (Chapter 3). The study population was nested in the overall cohort (Chapter 2), and included a total of 203 smear-positive TB patients who had successfully completed their TB treatment between 1996 and 2008 and were subsequently diagnosed and re-treated for smear-positive TB. To distinguish between relapse and reinfection, we compared DNA fingerprint patterns of *M.tb* strains re-cultured from diagnostic samples that had been routinely collected at the index and recurrent treatment episode of the same individual patient. DNA patterns were compared using restriction polymorphism (RFLP) analysis.

We found that of 130 recurrent smear-positive TB cases with paired DNA fingerprint results available, 64 (49%) had been due to relapse and 66 (51%) due to exogenous reinfection according to the study definition. The proportion of reinfection found in our study (51%) was lower than those reported from two earlier studies from the study setting. These studies had reported that exogenous reinfection was the underlying cause of recurrent TB after curative treatment in 12 (75%) of 16 [5] and in 24 (77%) of 31 recurrent TB patients [6].

The proportion of reinfection TB in our study was similar when restricting the study sample to documented HIV-negative recurrent TB cases (27 [51%] reinfections of 53 recurrences). This finding is in contrast to findings from two studies conducted in Malawi [13] and Gauteng Province in South Africa [9] which reported that reinfection TB occurred mainly among HIV-infected people whereas the majority of recurrences among HIV-uninfected people was due to relapse.

We estimated rates of relapse and reinfection TB over time since the previous TB treatment episode had been completed and found distinct temporal trends. The rate of relapse peaked at 4-5 months and was higher than the rate of reinfection TB during the first year after treatment completion (2.84% relapse vs. 0.73% reinfection), whereas reinfection dominated in the second (1.00% relapse vs. 1.17% reinfection) and the following years (year 3: 0.37% relapse vs. 1.18% reinfection). The observed temporal dynamics are consistent with findings from smaller studies in South Africa [9, 14] and China [15, 16] which reported that relapse had occurred early whereas reinfection TB involved longer time periods since the end of previous TB treatment. Relapse is likely to happen earlier, because TB due to reinfection involves additional time for individuals to become re-exposed and reinfected and is expected to occur more constantly over time.

Strengths and limitations

The strengths of the studies described in Chapter 2 and 3 include the use of a large set of TB program data and diagnostic samples from TB patients in a well-characterised high-incidence setting. The use of probabilistic record linkage allowed us to develop a retrospective cohort over a lengthy period (13 years). We conducted the largest molecular epidemiological study on relapse and reinfection TB in a high-incidence setting to date. While most earlier studies were limited to reporting proportions of reinfection TB among recurrent TB cases regardless of observation time, our study was large and long enough to estimate rates of relapse and reinfection TB over several years.

Several limitations apply to this work. It is based on routinely collected information. Although considerable efforts were made to assess the completeness and consistency of the data, for example through cross-checks with individual patient files, inconsistencies cannot be excluded. Treatment success in our study is based on programmatic definitions. This was a retrospective cohort study on the basis of treatment records without prospective follow-up.

Rates of TB observed in this study thus represent under-estimates of the true rates of TB after an episode of previous treatment because people may have developed TB again but returned for diagnosis, they may have been diagnosed and not have started treatment or started treatment elsewhere, and because the rate denominators include people who might have died or left the area.

The use of RLFP analysis in our study has limitations. “High resolution” methods such as whole genome sequencing would have been more powerful to discriminate between strains in order to distinguish between relapse and reinfection and to detect mixed strain infections. Misclassification of reinfection as relapse is likely if individuals became reinfected with the same strain, and we might thus have under-estimated the role of reinfection as a mechanism of disease recurrence. Alternatively, mixed strain infections may have led to misclassification if the initially underlying strain was selected and detected at recurrence.

An important limitation is the lack of information about HIV status in a large number of patients which precluded a complete analysis of the relationship between HIV infection and risks of recurrence and reinfection. Additional analysis (restricted to individuals with documented negative HIV status) suggested that HIV infection was not a primary driver of the observed association between time to recurrence and mechanism of recurrence.

However, restricting our data to HIV-negative individuals did not change the proportion of reinfection and the observed temporal dynamics. We are thus confident that the temporal trends as well as the high rates of reinfection cannot be explained by HIV status. Finally, drug susceptibility test results were poorly documented, and we were unable to study the role of drug-resistance towards TB among previously treated people.

Conclusions: previously treated TB in a high-incidence setting

The two studies provide novel insights into the frequency and dynamics of TB among previously treated people in a TB high-incidence setting.

They reveal a very high rate of smear-positive TB among people who were previously lost to follow-up from TB treatment. Nearly one third of these people were diagnosed with smear-positive TB and re-treated within two years. Moreover, more than one-third of those re-treated for smear-positive TB were lost to follow-up again during re-treatment. Improving adherence to a full course of TB treatment therefore remains an important principle to reduce the TB burden and associated transmission in this high-incidence setting. However, our data suggest that only a minority of diagnosed smear-positive TB is attributable to incomplete treatment.

People who successfully completed a previous TB treatment episode are still substantial risk of TB in this setting and constitute the majority of previously treated TB cases. We estimate that the rate of smear-positive TB after successful treatment exceeds several-fold the rate of smear-positive new TB in this setting. At least half of recurrences after successful treatment are due to reinfection, suggesting that the performance of TB treatment alone does not sufficiently explain the high rate of TB after successful treatment. Instead, individuals may be at elevated risk of becoming re-exposed and re-infected in the community or they may be especially susceptible to TB and progress more easily to active disease when reinfected [11, 17]. It is not known to what extent HIV infection may explain the high rates of recurrent TB due to reinfection. However, restricting the analysis to individuals with negative HIV status suggests that reinfection TB is common even among HIV uninfected people.

We describe for the first time the dynamics of relapse and reinfection TB over a lengthy time after previous successful TB treatment in a high-incidence setting. These temporal dynamics have several implications. They may partly explain the considerable variation in the contribution of reinfection to TB recurrence across multiple smaller studies with varying follow-up times (0-100%) [18]. The shorter the follow-up time (and the shorter the median time to recurrence) in these studies, the higher the probability that recurrence was due to relapse. Our findings are also relevant for the design of clinical trials of TB drugs, many of which are conducted in high-incidence settings. They support the need to reconsider follow-up

strategies. While shorting follow-up in trials requires higher sample sizes to estimate the risk of relapse, longer follow-up will increase reinfection TB as an undesirable outcome in the measure of the efficacy of drugs.

7.3. Modeling the impact of targeting TB control toward previously treated people in a high-incidence setting in Cape Town

We developed a transmission-dynamic mathematical model to investigate the population-level impact of two control interventions, targeted active case finding (TACF) alone and combined with secondary isoniazid preventive therapy (2°IPT) among people with a history of complete TB treatment (Chapter 4). The model was calibrated to data from the same high-incidence setting that had been the place of research for the first two studies (Chapter 2 and 3).

Rationale

The rational for TACF was preliminary evidence about the high rate of undetected prevalent TB in among previously treated people in this setting [4], suggesting that case finding efforts could be especially beneficial for this group. To our knowledge, TACF among former TB patients has not been considered for TB control in high-incidence settings.

The rationale for 2°IPT was the evidence that previously treated people were at high risk of developing a subsequent episode of TB, despite successfully completing a full course of TB treatment (Chapter 2) [19]. Among those successfully treated, a majority developed TB following exogenous reinfection (Chapter 3), suggesting that ineffective first-time TB treatment may not sufficiently explain the risk of recurrent TB. Evidence about the effect of 2°IPT existed from at least two earlier studies. A randomised-controlled trial in Haiti [20] had shown that 2ÎPT among HIV-infected people who had completed an episode of TB treatment reduced the rate of recurrent TB by 82%. A cohort study [21] among HIV-infected gold miners in South Africa had found that individuals with 2°IPT had a 55% lower rate of recurrent TB compared to those without.

The hypothesis that TACF and 2°IPT among previously treated people could yield population-level benefits for local TB control was based on findings of a high rate of TB in this subgroup, its relative large size in the population (~10% of adults [4]) observations that accounted for large proportions (>30%) of prevalent [4] and notified (incident) [3] TB cases in this setting.

Principles of impact

Before examining the key results of the mathematical modeling study, it is useful to revisit the anticipated *direct* and *indirect effects* of both targeted interventions in this high-incidence setting (see also Chapter 1, section 1.2.3. and Figure 1.2 for more details).

TACF is expected to reduce the time that those who already developed recurrent TB remain untreated (*direct effect*). TACF is also expected to reduce TB-associated mortality because infectious individuals are more promptly detected and thus less likely to die from TB (*direct effect*). Timely detection of recurrent TB is also expected to result in fewer transmission in the population (*indirect effect*).

Secondary IPT is expected to prevent recurrent TB after successful treatment (*direct effect*). In our model, we assumed a similar preventive effect of 2°IPT towards the rate of TB reactivation after treatment and the risk of disease progression following exogenous reinfection. The protective effect of 2°IPT is expected to be lost within months of cessation of therapy [22]. We therefore modelled a lifelong intervention with a drop-out rate of 15% per year (of people currently on 2°IPT). The stronger the direct preventive effect in the target group over time the lower the rate of novel infections in the population that may arise from contact with infectious target group members (*indirect effect*). Resultant reductions in TB incidence

and mortality are thus a consequence of both, directly preventing recurrent TB, and the reduction of transmission in the population.

Summary of key results

The model distinguished three different scenarios in the study setting – a baseline scenario (without additional interventions), a scenario of annual TACF as a single intervention, and a combined-intervention scenario of both annual TACF and 2°IPT. We projected that under the baseline scenario, a total of 4,879 (2,667 - 6,141) incident TB cases and 745 (274 - 956) TB-associated deaths will occur during the years 2016 - 2025. TB incidence would decline slowly under this scenario, at an average rate of 1.3% during this 10-year period.

Our study shows that interventions targeted among people who previously completed an episode of TB treatment could considerably accelerate this decline. We projected that the implementation of annual TACF reduced the time to detection among infectious individuals with a history of complete TB treatment by an average 4.2 months, from 9.3 (uncertainty interval: 2.4 - 17.4) months at baseline to 5.1 (2.0 - 7.1) months. TACF averted 14% (2% - 24%) of total incident TB cases and 24% (4 - 36%) of total TB deaths over the 10-year period in the total population. TACF combined with 2°IPT averted 44% (22% - 56%) of incident TB cases and 47% (11% - 58%) of TB deaths.

TACF had a larger effect on prevalence and mortality than on incidence, consistent with its effects. TACF does not directly reduce TB incidence among previously treated people. However, it reduces TB prevalence through finding and treating diseased individuals and mortality through reducing the time during which they remain untreated. Other than TACF, 2°IPT is expected to directly reduce TB incidence in the target group.

Sensitivity analyses indicated that less rigorous use of TACF and 2°IPT results in reduced impact. However, the data suggested a saturation effect of the interventions. Increasing the uptake of 2°IPT and the periodicity of TACF from a certain level onwards did not lead to a further increase in impact.

Strengths and limitations

The use of a calibrated transmission-dynamic mathematical model allowed us to assess the population-wide impact of interventions targeted towards a subgroup with high TB risk, and to project this impact over time. The study addresses an original and innovative research question at a time when novel interventions are urgently needed to strengthen TB control in high-incidence settings. However, this modeling study has several limitations.

The considerable uncertainty around our best projections of impact reflects the uncertainty of estimates of parameters describing the natural history of TB among people with and without a history of previous TB treatment. Parameters were selected from prior ranged using a Bayesian calibration approach [23]. This approach was used to obtain simulations that are consistent with “real data” and plausible ranges of model parameters. Setting-specific calibration data from various sources were used, including census data for the size of the local population, TB case notification data and TB prevalence survey data, and a local estimate of HIV prevalence. To avoid bias towards the estimates of impact, we made conservative assumptions about differences in the natural history of TB between treatment-experienced and treatment-naïve people which are reflected in wide prior parameter ranges.

The model was calibrated to data from a specific high-incidence setting: projections may not be readily generalisable to other high-incidence settings. Specifically, previously treated people represented a large population-subgroup in this setting that contributed considerably to the overall TB burden in this setting, an observation that is central to the projections of impact of interventions targeted toward this group. Data from other African settings show that the proportion of TB cases with a history of TB treatment may be lower compared to that observed in suburban Cape Town. For example, previously treated people accounted for only 13% of prevalent TB cases in Lusaka, Zambia [24], and for 15% in Nigeria [25], suggesting

that our projections of impact may not be readily generalisable to these settings. To date, the extent to which previously treated people contribute to the overall TB burden and associated transmission is poorly understood. We discuss two further studies that we conducted to better understand this extent in other settings (see section 7.4 below).

Other setting-specific conditions may limit the generalisability of our projections. We applied our modeling study to a suburban setting of 3.4 km^2 [1], with a resident population that is considered relatively stable [1, 6], with available transport and relatively short distances between resident homes and health-care facilities. Identifying, accessing, enrolling, and retaining individuals for the interventions may be considerably more challenging in rural areas because of distances and possible lack of infra-structure. Additional constraints to enrol and retain former TB patients may exist in settings where past TB treatment records are incomplete, or where the population is less stable. Furthermore, the projected impact depends is dependent on TB health-care seeking behaviour in settings. Our projections are therefore more likely to be generalisable to settings with similar challenges in finding and diagnosing TB patients and less to settings where there is less diagnostic and treatment delay.

We assumed a highly effective roll out of both interventions in this suburban setting. Specifically, we assumed that people who previously completed TB treatment were identifiable and accessible in this setting, and that that TACF was performed on average once per year in this group. We assumed that TB could be effectively detected during TACF, and that those in whom TB was diagnosed were timely referred to health-care and immediately initiated TB treatment. We also assumed high rates (90%) of 2°IPT initiation and an average 85% of annual retention. Less effective implementation of TACF and 2°IPT could reduce the impact that could be achieved in our setting. Potential challenges that may affect the successful roll-out of the interventions include that previously treated people may not be completely identifiable and accessible. The ability to effectively discriminate between diseased and non-diseased individuals depends on the availability and choice of screening tools and characteristics of the target population. Challenges affecting the effectiveness of 2°IPT include its uptake and retention, especially in the light of recent findings that the protective effect of IPT is likely to be lost after individuals drop out from treatment [22]. Prevalent infection with isoniazid and/or rifampicin-resistant strains of *M.tb* may reduce the efficacy of 2°IPT in the target group.

Finally, our study highlights the idea of a targeted control approach but does not include cost estimates of the targeted interventions and thus does not allow to determine their cost-effectiveness for TB control in relation to the status quo or alternative interventions. Further research is therefore needed to evaluate this approach (see section 7.7).

Main conclusions

This mathematical modelling study suggests that TACF and 2°IPT among previously treated people could have substantial population-level impact for TB control in this high-incidence setting. These targeted interventions could accelerate the declines in TB incidence and mortality in the local population, provided that they can be effectively implemented. The model suggests that the impact may decline over time, most likely because the pool of undetected prevalent TB [4] would be largest initially and reduced during the first few years after implementing the interventions. This saturation effect implies that the interventions modelled could form part of an adaptive control strategy in this setting. Such adaptive strategy, as emphasised by Yaesoubi and Cohen [26], would allow decision makers to use these targeted interventions temporarily (based on need) to make more efficient use of existing resources.

Our study constitutes a first step to understand the population-level impact of interventions targeted at previously treated people in high-incidence settings. Additional research is warranted to determine whether and under what conditions this targeted control approach could be feasible and effective to implement in high-incidence settings, and how its costs and benefits would compare to alternatives.

7.4. Burden of TB among previously treated people in other settings

The modeling study projected the population-level impact of interventions targeted at previously treated people in a TB high-incidence setting in suburban Cape Town (Chapter 3). A particular feature in this setting is that people with a history of previous TB treatment constitute a relatively large subgroup in the local population (~10% of adults [4]) and account for nearly one-third of notified TB cases every year [3]. A lung health survey in 2002 had found a high TB prevalence in this group (3.0% bacteriologically-confirmed TB) [4]. Of 26 bacteriologically-confirmed prevalent TB cases, 10 (38%) had a history of previous TB treatment, suggesting that this group may represent a large proportion of the undetected prevalent TB burden in this setting. This observation is relevant to the question of impact of interventions targeted among previously treated people. The higher the proportion of TB cases overall that arises from the target group, the higher the population-level impact that is theoretically achievable through preventive and case-finding efforts in this group (see Chapter 1, section 1.2.3 and Figure 1.4).

In this section, I summarise and discuss results from two further studies in which we explored whether epidemiological characteristics observed in Cape Town extend to other high-incidence settings in Southern Africa. Specifically, I investigated the extent to which previously treated contribute to the overall burden of prevalent TB (Chapter 5) and of notified (incident) TB (Chapter 6) in different settings.

Summary of key results

I made use of a large set of TB prevalence survey data from 24 South African and Zambian communities to estimate the prevalence of TB stratified for TB treatment history, and to investigate the extent to which previously treated people account for prevalent TB cases overall (Chapter 5). The prevalence surveys had been conducted for the primary outcome measure of the ZAMSTAR study, a large community-randomised trial [27].

A total of 90,601 adults had been enrolled in the surveys across all 24 communities. People with a history of previous TB treatment represented a variably large subgroup of the adult population in the communities. A total 7,362 (8.1%) adults reported a history of previous TB treatment (community range: 2.0% to 14.9%). The surveys found a total of 894 (1.39%) prevalent TB cases among 64,452 adults successfully evaluated for prevalent TB.

TB prevalence among treatment-experienced (previously treated) people was higher than that among treatment-naïve (not previously treated) people in most of the communities. In the 8 South African communities combined, it was 3.81 (95%CI: 3.25 – 4.47) per 100 treatment-experienced adults and 2.13 (1.96 – 2.31) per 100 treatment-naïve adults. In the 16 Zambian communities, TB prevalence was 1.01 (0.65 – 1.55) per 100 treatment-experienced adults and 0.53 (0.46 – 0.62) per 100 treatment-naïve adults. Stratification for HIV status showed that the difference in TB prevalence between both groups was restricted to the HIV-negative sub-population. TB prevalence among HIV-positive adults was 4.82 (95% CI 4.11–5.66) per 100 adults overall in the South African and 1.61 (95% CI 1.29–2.00) per 100 in the Zambian communities with no significant difference by TB treatment history.

The study showed that previously treated people represented a considerable proportion of the overall number of prevalent TB cases in some communities, especially in those with a high TB prevalence overall. This proportion was higher in the South African than in the Zambian communities (20.7% versus 10.4%) and exceeded 20% in nine communities overall (Figure 7.1).

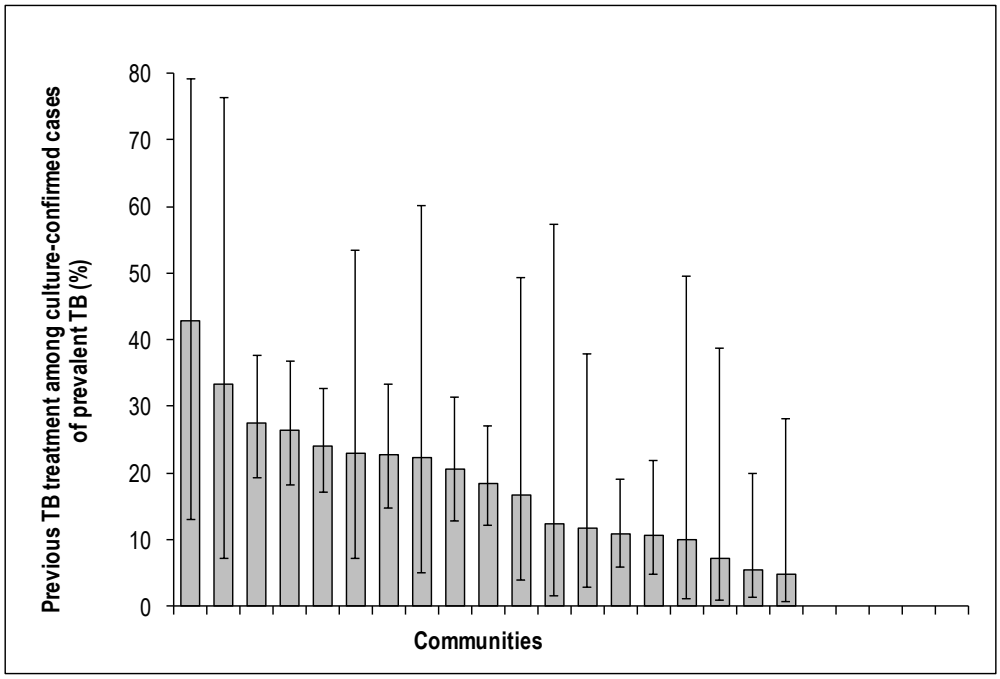

Figure 7.1. Data from the ZAMSTAR prevalence surveys: Proportion of prevalent TB cases detected who reported a history of previous TB treatment in 24 communities in Zambia and the Western Cape Province of South Africa (unpublished Figure).

In a further study (Chapter 6), we made use of electronic TB register data from the 52 South African health districts to investigate the proportion of previously treated individuals among notified, bacteriologically-confirmed TB patients.

The study showed that in 2011, a total of 182,455 bacteriologically-confirmed TB cases started TB treatment for (presumed) drug-susceptible TB in South Africa, of whom 35,633 (20%) had previously been treated for TB. Ecological analysis showed that previously treated individuals represented variable proportions, between 7.6% and 40%, of bacteriologically-confirmed TB patients treated in the districts in 2011. The proportion exceeded 20% in 17 of the 52 districts.

The majority of previously treated TB patients in the districts reported a history of previous successful treatment (median: 61%; inter-quartile range: 50% - 70%). Higher proportions of previously treated TB cases correlated with higher TB rates per 100,000 population (Spearman's correlation coefficient r=0.75; P<0.001) in the district population. The proportions of previously treated TB cases correlated inversely with estimates of HIV prevalence in the district population (r=-0.45; P<0.001) and with HIV co-infections among new TB patients (r=-0.70; P<0.001). Finally, we found that death rates during TB treatment (r=-0.29 [inverse]; P=0.035) and the rate of loss to follow-up from TB treatment (r=0.59; P<0.001) correlated with the proportions of TB patients that had been previously treated for TB.

Strengths and limitations

Both studies are based on large sets of data that provide unique opportunities to look at TB among previously treated people. Limitations of both studies include the secondary analysis of data that were collected during prevalence surveys (Chapter 5) and as part of the routine TB program (Chapter 6), which meant that we were unable to validate treatment history and other information. Treatment history was self-reported, and under-reporting of treatment history is likely – we may thus have under-estimated the true proportion of TB cases with a history of previous TB treatment. These were cross-sectional studies, and we were unable to investigate TB among previously treated people in relation to the timing of their previous treatment episode. We were also unable to determine the underlying causes and mechanisms for TB among previously treated people, e.g. to what extent poor quality or incomplete

treatment contributed to subsequent TB, and to what extent other risk factors played an important role. The lack of drug susceptibility data precluded investigation of drug resistance in the context of previously treated TB. The studies also provided limited opportunity to investigate the role of HIV-infection and ART towards the burden/rate of TB among previously treated people.

The ecological study was conducted at the level of the 52 health districts and did not allow us to draw conclusions about individual risk factors and mechanisms that lead to TB among previously treated people in the districts. We were unable to study other factors that may be associated with the burden of previously treated TB in the districts, such as drug-resistant TB, extensive disease, and the coverage of ART. Finally, we were unable to estimate TB case notification rates stratified by treatment history, because we did not have data available on the number of previously treated people in the population.

Main conclusions

Both studies show that previously treated people represent variable proportions of prevalent and incident (notified) TB cases in different settings. The particular characteristics in the Cape Town study setting (Chapter 2), where previously treated people contribute considerably to the overall number of TB cases applies to various other areas in South Africa and at least some communities in Zambia. Both studies (Chapters 5 and 6) from suggest that the proportion of previously treated TB is high especially in settings with a high background rate of TB. Here, larger numbers of people are treated for TB every year, and thus the subgroup of previously treated people that may give rise to TB cases may also be larger. We also speculate that higher rates of reinfection in areas with a high background rate of TB may preferentially increase the risk of TB among previously treated people if these represent a group that is more susceptible to TB than people who never suffered from TB before. Other factors such as the probability of survival before, during and after TB treatment (especially among HIV-infected individuals) or the quality of TB treatment may determine the burden of previously treated TB in different settings.

The analysis of prevalence surveys shows that in some communities, previously treated people represent large subgroups in the adult population and contribute considerably to the prevalent TB burden. Further research is needed to determine the conditions and mechanisms that lead to a high burden of previously treated TB in different settings. Understanding these conditions and mechanisms could help to decide what kind of control interventions among previously treated people could be most effective, and whether these targeted measures may be beneficial for TB control at the population-level in these settings.

7.5. Strengths and limitations of the dissertation as a whole

7.5.1. Strengths

A key strength of the research presented in this dissertation is the use of different analysis techniques (cohort analysis, cross-sectional and ecological analysis) and transmission-dynamic mathematical modeling to characterise the risk and burden of TB among previously treated people and to project the impact of interventions targeted at this group.

I had access to several large-scale TB epidemiological and programmatic data sets of different types and from various settings for this research. For example, I used 13-years TB treatment register data (Chapters 2-4) and a unique set of strain-type DNA fingerprint data for a large sample of TB patients (Chapter 3). Furthermore, I had access to a large set of TB prevalence survey data for more than 64,000 adults living in 24 different communities (Chapter 5) and another set of electronic TB register data for all of the 52 South African districts (Chapter 6). Additional data sources were available for the mathematical modeling study (Chapter 4) and

the ecological study (Chapter 6). The variety and size of these different datasets was a major strength of this work.

Finally, I conducted this research in collaboration with scientists/specialists from different institutions and with different backgrounds – among these were clinical and molecular epidemiologists, TB program experts, laboratory scientists and mathematical modelers. The exchange and collaboration within this network of people was another major strength of this work.

7.5.2. Main limitations

Important limitations across the different studies include the completeness and accuracy of routinely collected and survey data. For example, information about TB treatment history, central to this project, was usually self-reported by TB patients and survey participants. Under-reporting of treatment history [28] is likely, with various effects on the different studies presented. Other potential sources of error were incomplete and potentially inaccurate information about HIV status, bacteriological test results and treatment outcomes.

The data used did not allow to estimate the incidence rate of TB among previously treated people. Rates of TB after successful treatment and after loss to follow-up from treatment (Chapters 2 and 3) have to be interpreted and compared with caution as they do not include individuals with undiagnosed/untreated recurrent TB and because these rates also include individuals in the denominator (population at risk) who might have left the area or died.

The use of strain-type DNA fingerprinting/RFLP analysis to discriminate between endogenous reactivation and exogenous reinfection (Chapter 3) is limited by the relatively low power of this method to discriminate between different strains. Under-estimation of reinfection is also likely because individuals may have been reinfected with the same strain.

Another general limitation is the generalisability of findings from the Cape Town study setting (Chapters 2-4) including the projection from the mathematical model (Chapter 4; see also section 7.3). Additional research is therefore needed to characterise the rate and burden of recurrent TB, and especially of reinfection TB, as well as the potential of targeted control interventions in different populations (see also research recommendations, section 7.7).

Finally, the lack of data for known risk factors of recurrent TB precluded a more comprehensive assessment of TB among previously treated people. For example, I was unable to investigate the role of drug-resistance or that of HIV infection and ART for the development of TB among people with a history of previous TB treatment.

7.6. Summary of the evidence and its relevance

The research presented in this dissertation provides novel insights into (1) the risk and mechanisms of TB among people with a history of previous TB treatment, (2) the relevance of this high-risk group in the context of TB epidemics in Southern Africa and (3) the potential of targeting TB control interventions toward this group.

The findings about TB among previously treated people in a high-incidence setting in Cape Town extend previous knowledge from this and a limited number of other high-incidence settings in Southern Africa. Our studies were sufficiently large to describe the role of incomplete treatment and the dynamics of relapse and reinfection TB after successful treatment over a lengthy period. This work highlights the substantial risk of TB associated with loss to follow-up from TB treatment in a high-incidence setting and thus re-emphasises the necessity that TB control programs must ensure treatment adherence in order to prevent TB and associated transmission. However, due to the high burden of recurrent TB after apparently successful treatment, ensuring treatment adherence alone in high-incidence settings is unlikely sufficient to reduce TB among previously treated people.

This work describes, for the first time in a high-incidence setting, the distinct temporal dynamics of recurrent TB due to either endogenous reactivation (relapse) or exogenous reinfection, over a lengthy period of time since the completion of TB treatment. Consistent with earlier studies, I document reinfection TB as an important underlying mechanism for recurrent TB in this setting. The observed temporal dynamics are likely to help explain the substantial heterogeneity in the proportion of reinfection across observational studies [18]. Because reinfection is more common in later years, studies with shorter follow-up times are likely to under-estimate the true contribution of reinfection to recurrent TB. Studies should therefore consider follow-up time (study duration) when investigating relapse and reinfection TB.

Findings from this work are consistent with earlier reports [6, 11] suggesting that the rate of reinfection TB may exceed several-fold the rate of new TB, with important implications for TB control. High rates of reinfection TB over a lengthy time suggest that the performance of TB treatment alone is unlikely to explain the burden of recurrent TB in high-incidence settings. Instead, people with repeated episodes of TB are likely to represent a subgroup that is more likely to become re-exposed and/or that is generally more susceptible and thus more likely to become reinfected and to progress to active disease upon reinfection. Higher re-exposure would be important from a TB control perspective, as would indicate that TB case finding in personal networks may be beneficial to find and treat additional TB cases. Increased susceptibility would indicate that the degree of protective immunity conferred by a distant infection estimated among latently infected people [29] may not apply to individuals with a history of previous active TB. While several drivers of increased TB susceptibility in populations are already known (e.g. HIV, diabetes, alcohol, smoking), other factors such as the role pulmonary inflammation and impairment, chronic lung disease as well as genetic factors of susceptibility may contribute to TB susceptibility and the burden of recurrent TB in high-incidence populations. Understanding, determining and addressing the drivers of TB susceptibility may help tailoring additional TB control strategies more towards those at highest risk and therefore be of key importance for reducing transmission and the disease burden in high-incidence populations.

While high rates of recurrent TB have been documented in earlier work [19], the research presented here links the high risk among people with a history of previously treated TB to the overall TB burden in the communities. It identifies several high-incidence communities (and districts) where previously treated individuals represent a group that contributes substantially to prevalent and incident TB. Although onward transmission from previously treated people was not directly measured in this research, the fact that this group accounts for relatively large fractions of the overall disease burden in several settings is consistent with the hypothesis that this group may also contribute substantially to transmission, especially in populations with the highest TB incidence.

The mathematical modeling study addresses an innovative idea at a time when better strategies are urgently needed to reduce transmission and the TB burden in populations with a high incidence of TB. It suggests considerable public health potential in high-incidence settings for TB control interventions targeted among previously treated people. These findings constitute a first step towards exploring these targeted interventions as a strategy to enhance TB control, particularly in settings of persistent TB epidemics where conventional TB control has failed to achieve population-level impact. The findings from this study suggests the importance of further research to explore the feasibility, impact and cost-effectiveness of this targeted strategy in different high-incidence settings (section 7.7).

7.7. Recommendations for future research

Research is necessary to advance TB control at global level and particularly in TB- and HIV-endemic settings in the forthcoming years. Key research priorities include the development of novel TB drugs, diagnostics and vaccines [30]. In high-incidence settings, research will need to address *M.tb* transmission to help significantly reduce TB morbidity and mortality. Innovative

novel strategies are required to reduce transmission while minimising additional demands to impoverished people and resource-constrained health systems [31]. A focus on individuals and groups at highest risk (and burden) of TB may thereby be crucial. These high-risk groups include, among others, people with a history of previous TB treatment.

Specific recommendations for further research can be made on the basis of the research findings presented in this dissertation. Additional research is necessary to confirm the role of reinfection as a mechanism for recurrent TB in different settings, and to establish the underlying causes of high reinfection TB rates. More studies are needed to understand the role of reinfection in the cause of recurrent TB among HIV-infected and -uninfected people. Specifically, more research is needed to understand whether high rates of re-infection TB among successfully treated people are due to a higher rate of re-exposure in communities, or whether their individual susceptibility drives their risk of TB. Additional research may aim at establishing clinical, genetic and immunological markers [32] of susceptibility among previously treated people which may help to improve our general understanding about heterogeneity in TB risk. Those markers would also allow to identify individuals at highest risk who might benefit more from intensified control measures than others. Studies should also investigate whether recurrent TB is associated with the acquisition of drug-resistance in high-incidence settings.

Future research should, however, move beyond the documentation of risk factors and mechanisms that lead to recurrent TB in high-incidence settings. Operational research in settings where relapse is common may help to address and correct health system inefficiencies such as irregular or inadequate treatment, undetected drug-resistance and inconsistent monitoring of treatment outcomes. Trials and implementation studies are warranted to determine the feasibility, effectiveness and cost-effectiveness of different strategies to prevent recurrent TB. These strategies may focus on individuals at highest risk of recurrence including those with extensive (and cavitary) disease, people living with HIV and those with drug-resistant TB [19]. A variety of different strategies may be considered, including measures to reduce interruptions/irregular treatment, individualised and/or extended TB treatment, adjuvant immunotherapy [33], post-TB treatment vaccination and secondary preventive therapy. Studies should also focus on interventions to prevent loss of follow-up during TB treatment, for example through reminders and patient support systems. Research is also needed to identify feasible and effective ways to find and treat recurrent TB earlier. Previously treated individuals attending health-care in high-incidence settings should be considered for systematic screening as recommended by the WHO [34]. Studies may also help optimise diagnostic algorithms to reliably detect TB among previously treated people. Finally, research should aim to evaluate the population-level impact and cost-effectiveness of targeting control measures at previously treated people. The costs and benefits of these interventions need to be weighed against other strategies for reducing transmission and the disease burden in populations severely affected by TB epidemics.

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Glossary of terms and abbreviations

Active TB Case Finding (ACF)

Efforts to screen for active TB among individuals who did not (yet) self-present to health-care services for diagnosis.

Case Fatality Ratio (CFR)

The case fatality ratio describes the number of tuberculosis deaths relative to the number of incident tuberculosis cases and is usually expressed as a percentage.

Directly-Observed Treatment, Short-course (DOTS) Strategy

Official name of the international tuberculosis control strategy launched by the WHO in the 1990s.

Extensively drug-resistant TB (XDR-TB)

A type of tuberculosis that is resistant to isoniazid and rifampicin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Multidrug-resistant TB (MDR-TB)

A type of tuberculosis that is resistant to at least isoniazid and rifampicin.

Passive TB case finding (passive TB case detection)

Tuberculosis that is detected among symptomatic individuals who self-present to health-care services for diagnosis.

Previously treated person / TB case

A person / TB case who had previously received at least 1 month of standard TB treatment

Recurrent TB

Tuberculosis that re-occurs after an individual had been considered successfully treated. Recurrent TB may be due to endogenous reactivation (relapse) or exogenous reinfection with *Mycobacterium tuberculosis*,

Relapse

Endogenous reactivation of TB (see 'Recurrent TB'). Note: In routine TB recording and reporting, term 'relapse' is used by the World Health Organization for every recurrent TB cases after previous successful treatment, i.e. without distinguishing endogenous reactivation from exogenous reinfection.

Secondary Isoniazid preventive therapy

Isoniazid preventive therapy that is administered post-TB treatment and intended to prevent recurrent TB.

Targeted Active Case Finding (TACF)

Active TB case finding (ACF) in a pre-defined target group

TB treatment-experienced person / TB case

A person / TB case who had previously received at least 1 month of standard TB treatment

TB treatment-naïve person / TB case

A person / TB case who had never received at least 1 month of standard TB treatment

Tuberculosis (TB) burden

In this dissertation, the tuberculosis burden refers to the absolute number of tuberculosis cases.

Appendix: Supplementary information document for the mathematical model

Modeling the impact of tuberculosis control interventions targeted to previously treated people

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Contents

S1. Study setting

Our study focuses on two adjacent suburban communities with a high tuberculosis (TB) burden in Cape Town, South Africa, covering an area of 3.4 km², and with a total population of 39,930 people in 2011. The internationally-endorsed TB control strategy (DOTS) was introduced in these communities in 1996. In the first year of the program, the rate of notified TB (all forms) was 1,340 cases per 100,000 residents [1]. Treatment success rates were initially low but increased rapidly and exceeded 80% amongst smear-positive TB cases in 2003 [2]. However, persistently high annual rates of infection (estimated 3.7% in 1999 and 4.1% in 2005 [2]) suggest that control measures, while improving individual outcomes, did not reduce transmission [3]. High local rates of recurrent TB after previous successful treatment [4-6] and after loss to follow-up from treatment [7] have also been reported; a lung health survey conducted in 2001 identified a high prevalence of undetected TB among previously treated residents [8].

S2. Model structure

Childhood subcomponent: At birth, individuals enter the childhood subcomponent of the TB model (Figure S1) in the susceptible state (S_{Ch}), where they face a time-varying risk of infection, conditional on the force of infection which is dependent on the total number of infectious cases (adults and children) at time t. Upon primary infection, children either progress rapidly to infectious TB (I_{Ch}) or reach a latently infected (non-infectious) state (L_{Ch}). Children may remain in the latent state, or their infection may reactivate and progress to infectious TB (I). They may also become reinfected and either rapidly progress to infectious disease or remain in the latent state. Upon infectious disease, children may move into a recovered (R_{Ch}) state after being found and treated.

At any state, children may leave the model subcomponent into the main (adult) component at rates reflecting their age progression beyond 14 years (Figure S1). Specifically, children transit from the susceptible (S_{Ch}) state into the adult treatment-naïve susceptible state (S_{TN}), from the latently infected state (L_{Ch}) into the adult treatment-naïve latently infected state (L_{TN}), and from the infectious state (I_{Ch}) into the adult treatment-naïve infectious state (I_{TN}). We assume that treatment of childhood TB is always complete, thus, children in the recovered state (R_{Ch}) move into the adult latently infected after complete treatment state (L_{TC}).

Main component (adults): Treatment-naïve susceptible adults transition from the susceptible state (S_{TN}) to the latently infected state (L_{TN}) or directly into the infectious TB state (I_{TN}) after primary infection (Figure 1, main manuscript). Latently infected treatment-naïve adults (L_{TN}) may experience reactivation disease and transition into the infectious TB state (I_{TN}). If reinfected while in the latently infected state (L_{TN}), they may progress to infectious disease (I_{TN}) or remain latently infected (L_{TN}). Treatment-naïve infectious adults (I_{TN}) may be identified and move into either of the two treatment compartments (TC: treatment that is completed, TI: treatment that is incomplete). The transition into these two treatment states is determined by the case finding rate and the proportion of complete treatment among new (i.e. previously treatment-naïve) TB cases estimated for the study setting. Individuals in the incomplete treatment state (TI) move into a treatment-experienced latently infected state (L_{TI}) or, upon continuous infectious TB, directly into the infectious TB (I_{TI}) state. From latent infection, they may progress to infectious TB (I_{TI}) either via disease reactivation or following reinfection. Upon complete treatment (TC), all adults transition to a latently infected state (L_{TC}) (i.e. consistent with many TB models, we assume that sterilizing cure is not achieved). We introduced two different states of latent infection for those individuals completing treatment: L_{TC} and $L_{TC\ 2°IPT}$. This allows us to distinguish whether individuals were enrolled in 2°IPT. Latently infected adults after complete treatment (L_{TC} and $L_{TC\ 2°IPT}$) may progress to infectious disease (I_{TC}) either via reactivation or following reinfection. Similar to treatment-naïve infectious cases (I_{TN}), cases occurring after either incomplete (I_{TI}) or complete treatment (I_{TC}) move back into the two treatment states (TI and TC) at rates determined by case finding rates and the proportion of complete treatment estimated for the study setting. We implemented an active case finding rate, incremental to the passive case finding rate, to simulate TACF among adults who previously completed TB treatment. Individuals may exit the model due to death from any state, with additional excess mortality rates due to TB disease and HIV infection implemented in out model.

Model subdivisions for HIV co-infection and antiretroviral treatment: Upon HIV infection (Figure 1, main manuscript), HIV-negative adults (HIV-) transit into a non-immunocompromised HIV infected state (HIV+NIC), and upon progression, into an immunocompromised (HIV+IC) subdivision. Upon initiation of ART, individuals in either of the two prior HIV+ subdivisions may transit into a fourth subdivision (HIVART). Once initiated on ART, individuals were assumed to stay on ART. We did not model HIV in children.

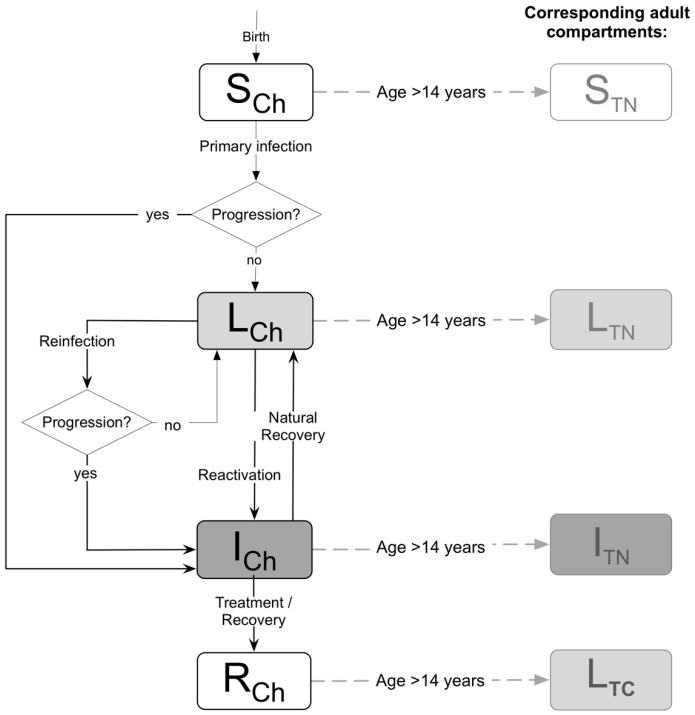

Figure S1: Model subcomponent for children aged 0-14 years
Abbreviations: S = Susceptible; L = Latently infected; I = Infectious; R = Recovered; not shown: mortality rates; dashed arrows indicate age transition into the corresponding compartments of the adult component of the model (see Figure 1, main manuscript)

S3. Model parameterization

Parameter values and ranges used in the model along with their sources are provided in the subsequent sections and Tables S1-S14. Rates shown are per year unless otherwise specified.

S3.1. Demographics

Estimates for demographic parameters are based on data from the Tygerberg sub-district of Cape Town in which the study setting is situated. We assumed a constant birth rate throughout the study period which was estimated by dividing the number of life births in the study setting reported for the year 2003 [9] by the projected population in 2003 (Table S1). Estimates of the natural death rates among children 0-14 years of age were derived from unpublished mortality data (for 2011) provided by the City of Cape Town Directorate of Health (Table S1). In the absence of published data, we derived an estimate of the natural mortality rate among adults through calibration, allowing for a 1.0% annual population growth, consistent with unpublished census data for the study setting (Table S1). We assumed that the rate of natural death among treatment-experienced adults was between equal and 5-times higher compared to treatment-naïve adults. This range takes into account the possibility that mortality among former TB patients may be higher [10-12] due to a variety of factors such as lung impairment and chronic pulmonary disease [13] and an elevated risk of death from lung cancer [14] compared to individuals without a history of TB.
We assumed that on average, a child would be in contact with 40 other children and 9 adults per day, and an adult would be in contact with 15 adults and 9 children per day [15].

Table S1: Model Parameters – Demographics

Measure	Value [Interval]	Source
Annual birth rate	0.0189	[9]
Annual population growth	1.0%	estimated from unpublished census data, City of Cape Town
Annual natural death rate among children (<15 years)	0.0017	estimated from unpublished census data, City of Cape Town
Annual natural death rate among adults (≥15 years)	0.009 [0.0086-0.0096]	from calibration
Natural death rate ratio, TB treatment-experienced adults to treatment-naïve adults	[1-5]	assumption

S3.2. Natural history of TB

Estimates for transition rates between TB-related states were derived from the published literature, where available (Tables S2-S5). In accordance with prior modeling studies, we considered that distant prior (latent) infection would lead to partial immunity reducing the risk of becoming reinfected (Table S4). Parameters for HIV-infected adults take into account that HIV alters the natural history of TB. Specifically, HIV-infected individuals are subject to a higher probability of fast progression to active TB following infection [16, 17] (Table S2) and a higher probability of reactivation of latent infection [18] (Table S3).

We assumed that children were less likely to transmit TB by the ratio 0.12 [0.034-0.305] (compared to treatment-naïve adults) that was based on the probability of smear-positive TB among children and adults estimated in a recent meta-analysis [19].

Table S2: Model Parameters - Probability of Fast Progression to Active TB Upon Primary Infection

Subgroup	Value [Interval]	Source
Adults, susceptible/treatment-naïve/HIV-	0.115 [0.09-0.14]	[20-22]
Adults, susceptible/treatment-naïve/HIV+/non-immunocompromised	0.33 [0.18-0.51]	[20-22]
Adults, susceptible/treatment-naïve/HIV+/ immunocompromised	0.805 [0.75-0.91]	[20-22]
Children, susceptible	0.118 [-]	estimated from [23]

Table S3: Model Parameters - Rate of Reactivation of latent TB infection

Subgroup	Value [Interval]	Source
Adults, latently infected/treatment-naïve/HIV-	0.001 [0.0003-0.0024]	[21, 22, 24, 25]
Adults, latently infected/treatment-naïve/HIV+/non-immunocompromised	0.003 [0.001-0.006]	[21, 22, 24, 25]
Adults, latently infected/treatment-naïve/HIV+/ immunocompromised	0.1275 [0.080-0.200]	[21, 22, 24, 25]
Children, latently infected	0.001 [0.0003-0.0024]	assumption

Table S4: Model Parameters – Percent Reduction in the Risk of becoming Reinfected due to Partial Immunity afforded by Prior Infection

Subgroup	Value [Interval]	Source
Adults, latently infected/treatment-naïve/HIV-	0.65 [0.37-0.87]	[22, 24, 26-28]
Adults, latently infected/treatment-naïve/HIV+/non-immunocompromised	0.45 [0.23-0.68]	[22, 24, 26-28]
Adults, latently infected/treatment-naïve/HIV+/ immunocompromised	0.25 [0.14-0.39]	[22, 24, 26-28]
Children, latently infected	0.65 [0.37-0.87]	assumption

Table S5: Model Parameters – Rate of Natural Recovery among Undetected Active TB Cases

Subgroup	Value [Interval]	Source
Adults, infectious/treatment-naïve/HIV-	0.2 [0.15-0.25]	[21, 22, 26, 29]
Adults, infectious/treatment-naïve/HIV+/non-immunocompromised	0.1 [0.06-0.16]	[21, 22, 26, 29]
Adults, infectious/treatment-naïve/HIV+/ immunocompromised	0	[21, 22, 26, 29]
Children, infectious	0.2 [0.15-0.25]	assumption

S3.3. Natural history of TB: Characteristics of treatment-experienced adults

The model allows for specific characteristics in the natural history of TB among individuals previously treated for the disease. In the absence of published estimates for many of these parameters, we specified prior parameter ranges and derived posterior parameter values through calibration (see below).

We assumed that TB treatment-experienced people were equally likely to be exposed to an individual with infectious TB in the community compared with treatment-naïve people. However, we allowed treatment-experienced adults to differ from treatment-naïve, latently infected adults in terms of their risk of becoming reinfected upon exposure. This was achieved through differential parameters for partial immunity towards reinfection among treatment-experienced and treatment-naïve people derived through calibration (same prior ranges; Table S6, see Table S4 for comparison). Rates of reactivation TB after complete and incomplete treatment were derived from calibration. To account for the possibility of higher reactivation rates after prior treatment for active TB, we specified prior parameter ranges for reactivation rates (Table S7) with the lower boundary being equal and the upper boundary 20-times higher than that for reactivation of distant prior latent infection (compare Table S3).

Based on findings from prevalence surveys that treatment-experienced cases of TB were more likely to be coughing and to be smear-positive [30], we assumed that treatment-experienced TB cases were up to 1.5-times more likely to transmit TB compared to treatment-naïve TB cases in terms of their potential to transmit TB.

Individuals with incomplete treatment may continue to suffer from infectious disease. Based on data from a retrospective cohort study conducted previously in the study setting [7], we assumed that between up to 20% of those who were lost to follow-up during treatment remained infectious (or rapidly relapsed) and thus moved directly into the compartment of infectious TB (Table S8).

Table S6: Model Parameters –Percent Reduction in the Risk of becoming Reinfected due to Partial immunity after (previously treated) active TB

Subgroup	Value [Interval]	Source
Adults, latently infected/prior complete or incomplete treatment/HIV-	- [0.37-0.87]	[22, 24, 26-28]
Adults, latently infected/ prior complete or incomplete treatment/HIV+/non-immunocompromised	- [0.23-0.68]	[22, 24, 26-28]
Adults, latently infected/ prior complete or incomplete treatment/HIV+/ immunocompromised	- [0.14-0.39]	[22, 24, 26-28]

Table S7: Model Parameters – Rate of Reactivation after TB treatment

Subgroup	Value [Interval]	Source
Adults, prior complete treatment/HIV-	0.001 [0.0003-0.048]	see: S3.2
Adults, prior incomplete treatment/HIV-	0.001 [0.0003-0.048]	see: S3.2
Adults, prior complete treatment /HIV+/ non-immunocompromised	0.003 [0.001-0.06]	see: S3.2
Adults, prior incomplete treatment /HIV+/non-immunocompromised	0.003 [0.001-0.12]	see: S3.2
Adults, prior complete treatment/HIV+/ immunocompromised	0.1275 [0.080-2.00]	see: S3.2
Adults, prior incomplete treatment /HIV+/ immunocompromised	0.1275 [0.080-4.00]	see: S3.2

Table S8: Model Parameters – Probability of Persistent Active TB (or Rapid Relapse) Following Incomplete Treatment

Subgroup	Value [Interval]	Source
Adults, susceptible/prior incomplete treatment/any HIV-status	[0-0.20]	based on data from [7]

S3.4. TB case detection and treatment

Parameters for TB case detection rates were derived from calibration. We allowed for shorter times to detection assuming that people who had experienced TB treatment may seek care more promptly again than those without previous TB treatment. We also assumed shorter times to detection for HIV-infected people (Table S9). The prior ranges used were informed by estimates of infectious disease duration before detection from previous studies in South Africa [31] and Zimbabwe [32].

We assumed that TB cases on treatment are non-infectious, i.e. they do not contribute to transmission. The duration of complete treatment among new and re-treatment cases was estimated from treatment register data (Table S10). We assumed that treatment is either complete or incomplete. Proportions of complete treatment among treatment-naïve and treatment-experienced people between 1996 and 2008 were estimated from the TB treatment register data (Table S11). For the years following 2008, we randomly sampled treatment completion probabilities from a uniformly distributed range of probabilities specified by the 1996 to 2008 data.

Table S9: Model Parameters – Baseline time between disease onset and detection (years)

Subgroup	Value [Interval]	Source
Adults, infectious/treatment-naïve/HIV-	[0.083-3]	assumption
Adults, infectious/ or prior complete or incomplete treatment/HIV-	[0.083-2]	assumption
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV+	[0.083-2]	assumption
Children, infectious	[0.083-3]	assumption

Table S10: Model Parameters – Duration of treatment (years)

Subgroup	Value [Interval]	Source
Adults, complete treatment	0.50 (0.47-0.57)	TB program data
Adults, incomplete treatment	0.42 (0.31-0.52)	TB program data

Table S11: Probability of complete treatment

Subgroup	**Year**							**Source**
	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	
Adults, treatment-naïve	91 (87-94)	98 (95-99)	97 (94-98)	94 (90-96)	97 (94-98)	99 (96-99)	98 (96-99)	TB program data
Adults, prior complete treatment	92 (82-97)	92 (83-96)	92 (85-96)	94 (86-97)	88 (79-94)	94 (87-98)	89 (80-94)	TB program data
Adults, prior incomplete treatment	60 (37-79)	84 (60-95)	82 (56-94)	65 (40-84)	83 (58-95)	55 (33-75)	77 (46-93)	TB program data

S3.5. TB-associated (excess) mortality

We considered excess mortality rates (incremental to natural death rates) for two different groups, those with untreated active (infectious) TB (Table S12) and those on TB treatment (Table S13). We assumed that the excess mortality rate among HIV-infected non-immunocompromised adults and those HIV-infected on ART was similar to that among HIV-uninfected individuals. We further assumed that the excess mortality rate among untreated children was similar to that among HIV uninfected adults, and that children would not die from TB while on treatment (Table S13).

Table S12: Model Parameters – Rate of TB-associated (excess) mortality rate, untreated TB

Subgroup	Value [Interval]	Source
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV-	0.28 [0.20-0.37]	[21, 22]
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV+/non-immunocompromised	0.28 [0.20-0.37]	assumption, see S3.5
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV+/ immunocompromised	0.80 [0.47-1.27]	[22, 33, 34]
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV+/ART	0.28 [0.20-0.37]	assumption, see S3.5
Children, infectious	0.28 [0.20-0.37]	assumption, see S3.5

Table S13: Model Parameters – Rate of TB-associated (excess) mortality rate, on TB treatment

Subgroup	Value [Interval]	Source
Adults, infectious (any subcategory)	0.056 [0.047-0.070]	estimated from TB program data
Children, infectious	0	assumption

S3.6. Natural history of HIV infection

Adults may be infected with HIV at any state in the model and move across the HIV subdivisions. The rate of HIV transmission in the adult population was derived from calibration. Rates of progression from non-immunocompromised to immunocompromised HIV and that of HIV-associated excess mortality among non-immunocompromised people were estimated from data published in the literature (Table S14). The distinction between *non-immunocompromised* and i*mmunocompromised* HIV-infected adults was made on the basis of CD4 count cut-off level of <350/mm³. HIV-associated excess mortality among immunocompromised people was calculated from estimates of survival time among HIV-infected people not on ART, assuming that 75% of these died from HIV-related causes other than TB. It was assumed that all children in the study setting were and remained HIV uninfected.

Table S14: Model Parameters – Rate of TB-associated (excess) mortality rate, untreated TB

Measure	Value [Interval]	Source
Annual rate of progression to immunocompromised HIV from non-immunocompromised HIV	0.142 [0.135-0.149]	[35]
Survival time of HIV-infected people not on ART (years)	10.2 [9.7-10.5]	[36]
Annual non-immunocompromised HIV-associated excess mortality rate	0.008 [0.005-0.012]	[22, 37-41]
Annual immunocompromised HIV-associated excess mortality rate	0.068 [0.062-0.074]	calculated from estimated survival time, see above
Annual HIV-associated excess mortality rate while on ART	0.008 [0.005-0.012]	[22, 37-41]
Effectiveness of ART in reversing effect of HIV on TB natural history (compared to the HIV+/non-immunocompromised state, excluding mortality)	0.69 [0.47-0.81]	[42]

S3.7. Initiation of antiretroviral treatment among HIV-infected adults

Assumptions were made to consider ART initiation among HIV-infected people in the study setting.
ART among immunocompromised adults not on TB treatment. We assumed a (historical) rate of ART initiation among immunocompromised people of 0.1 per year in 2004, the year of ART roll-out in Cape Town, and a linear increase of this rate to 0.3 per year in 2016, after which the rate remains constant.
ART among non-immunocompromised adults not on TB treatment. Considering the possibility that ART is also offered to HIV-infected people above a CD4 count of 350mm³, we assumed a rate of ART initiation among non-immunocompromised people of 0.02 per year in 2004, and a linear increase of this rate in the following years to 0.1 per year in 2016, after which the rate remains constant.
ART among immunocompromised and non-immunocompromised adults starting TB treatment. In line with national TB guidelines for South Africa, it was considered that ART is also initiated when HIV-infected people start TB treatment. We assumed that ART was initiated among 10% of HIV-infected individuals starting TB treatment. This proportions increases linearly to 30% until 2016 and remains

constant at 30% in the following years. We assumed that ART was initiated at the start of TB treatment but was not initiated at a later stage during the course of TB treatment.
Figure S2 shows the projected coverage of ART among treatment-naïve and treatment-experienced HIV-infected adults (not on TB treatment) over time derived from our model.

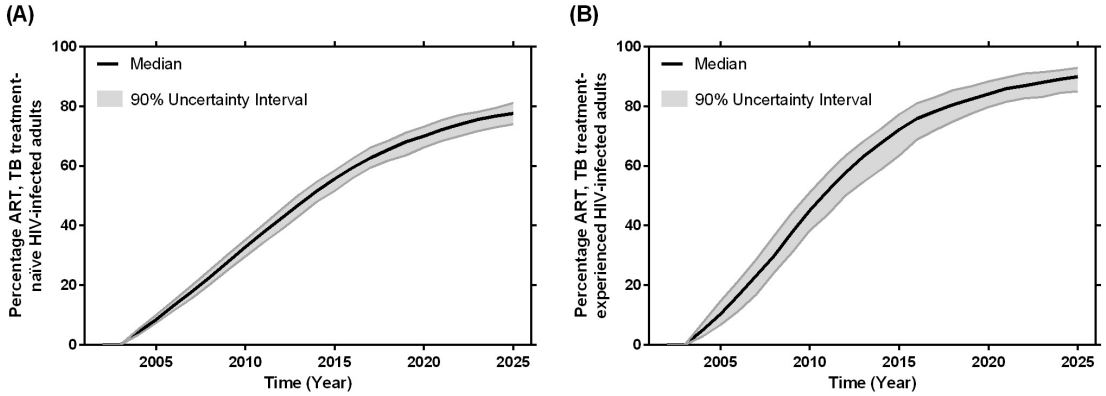

Figure S2. Projected coverage of antiretroviral treatment (ART) among HIV infected adults, 2004 - 2025
Panel A: treatment-naive adults
Panel B: treatment-experienced adults

S4. Simulation approach

Let $\lambda_{i\leftarrow i'}$ denote the rates at which members of age group $i \in \{\text{Ch, Ad}\}$ contact members of age group $i' \in \{\text{Ch, Ad}\}$ and let $H = \{\text{I}_{\text{TN}}, \text{I}_{\text{TI}}, \text{I}_{\text{TC}}\}$ denote the set of adult compartments with infectious status. We used $N_{\text{Ch}}(t)$ and $N_{\text{Ad}}(t)$ for the number of children and adults at time t, and $N_h(t)$ for the number of population members in model compartment h.

We defined the force of infection for susceptible and latent children ($h \in \{\text{S}_{\text{Ch}}, \text{L}_{\text{Ch}}\}$) at time t as:

$$F_h(t) = \beta_h \left(\lambda_{\text{Ch}\leftarrow\text{Ch}} \frac{N_{\text{I|Ch}}(t)}{N_{\text{Ch}}(t)} \eta_{\text{I|Ch}} + \sum_{h' \in H} \lambda_{\text{Ch}\leftarrow\text{Ad}} \frac{N_{h'}(t)}{N_{\text{Ad}}(t)} \eta_{h'}\right), \quad (1)$$

and for susceptible and latent adults ($h \in \{\text{S}_{\text{TN}}, \text{L}_{\text{TN}}, \text{L}_{\text{TC}}, \text{L}_{\text{TI}}\}$) as:

$$F_h(t) = \beta_h \left(\lambda_{\text{Ad}\leftarrow\text{Ch}} \frac{N_{\text{I|Ch}}(t)}{N_{\text{Ch}}(t)} \eta_{\text{I|Ch}} + \sum_{h' \in H} \lambda_{\text{Ad}\leftarrow\text{Ad}} \frac{N_{h'}(t)}{N_{\text{Ad}}(t)} \eta_{h'}\right). \quad (2)$$

In above equations, β_h is the relative susceptibility of members in compartments $h \in \{\text{S}_{\text{Ch}}, \text{L}_{\text{Ch}}, \text{S}_{\text{TN}}, \text{L}_{\text{TN}}, \text{L}_{\text{TC}}, \text{L}_{\text{TI}}\}$ with respect to susceptibility of treatment-naïve adults (we set $\beta_{\text{S|Tn}} = 1$), and η_h is the infectivity of members in infectious compartment $\{\text{I}_{\text{Ch}}, \text{I}_{\text{TN}}, \text{I}_{\text{TI}}, \text{I}_{\text{TC}}\}$. Based on existing survey data, we assumed $\lambda_{\text{Ch}\leftarrow\text{Ch}} = 4.7$, $\lambda_{\text{Ch}\leftarrow\text{Ad}} = \lambda_{\text{Ad}\leftarrow\text{Ch}} = 3.1$ and $\lambda_{\text{Ad}\leftarrow\text{Ad}} = 10.7$.
To generate realizations for the number of new infection during the period $[t, t + \Delta t]$ among susceptible and latent children (compartments S_{Ch} and L_{Ch}), and among susceptible and latent adults (compartments S_{TN}, L_{TN}, L_{TI}, and L_{TC}), we sampled from binomial distributions $Binomial(N_h(t), 1 - \exp(-F_h \Delta t))$, $h \in \{\text{S}_{\text{Ch}}, \text{L}_{\text{Ch}}, \text{S}_{\text{TN}}, \text{L}_{\text{TN}}, \text{L}_{\text{TC}}, \text{L}_{\text{TI}}\}$.
Members of some compartments may leave the compartment due to multiple competing events; for example, members of compartment L_{TN} may leave due to reactivation of latent infection, reinfection, or natural death. To generate realizations for the number of individuals leaving these compartments during the period $[t, t + \Delta t]$ due to each event, we sampled from multinomial distribution $Multinomial(N_h(t), 1 - \exp(-r_1 \Delta t), 1 - \exp(-r_2 \Delta t), \ldots, 1 - \exp(-r_R \Delta t))$ where $N_h(t)$ is the size of the compartment and $r_1, r_2, \ldots, r_R$ are the rates of these competing events.

S5. Model calibration

S5.1. Calibration data sources

We calibrated the model to data from three main sources. Population census data provided by the City of Cape Town were used to obtain estimates of the size and age structure (i.e. children vs. adults) of the population in the study setting. Data from a lung health prevalence survey conducted in the study setting in 2002 [8] were used to derive estimates of the proportion of adults with a history of previous TB treatment and of the prevalence of TB among treatment-naïve and treatment-experienced adults in 2002. Estimates of the crude prevalence of TB by treatment history were calculated from [8] by dividing each, the number of treatment-naïve and treatment-experienced adults detected with culture-confirmed TB by the total number of adults in the survey sample multiplied by each, the proportion of treatment-naïve and treatment-experienced adults in the survey sample, respectively. Finally, we accessed TB treatment data from an electronic TB treatment register database that had been cleaned for duplicate entries and assessed for data consistency to obtain the number of new and previously treated TB cases registered for treatment in the study setting. The proportion of new and previously treated TB patients with complete TB treatment was estimated among new and previously treated TB cases by dividing the number of TB cases with documented treatment outcome success by the total number of patients with either treatment success or loss to follow-up (formerly termed 'treatment default', defined as treatment interruption for at least two consecutive months) in that particular year (i.e. thereby excluding TB cases with treatment failure, transfer out or unknown treatment outcome from the denominator).

To estimate parameters of HIV transmission in the community, we calibrated the model to an estimated HIV prevalence of 5.2% (4.0%-6.0%) among adults living in the study setting in 2002, assuming that HIV-prevalence was half of the 2002 antenatal survey estimate for the greater Tygerberg East Sub-district.

Calibration targets, data sources, and specified feasible ranges are shown in Tables S15-S17.

Table S15: Calibration Targets for 2002

Target	Value [Interval]	Source
Number of adults in the study setting	25,903	City of Cape Town
Number of children in the study setting	10,427	City of Cape Town
Percentage treatment-experienced, all adults	9.7 [8.7-10.9]	[8]
Percentage prevalent TB, treatment-naive adults	0.51 [0.26-0.76]	[8]
Percentage prevalent TB, treatment-experienced adults	2.99 [1.14-4.77]	[8]

Table S16: Time-varying calibration targets (2002 -2008)

Target	**Value [Interval]**							**Source**
	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	
Number of treatment-naïve adults starting TB treatment	172	234	200	224	216	233	210	TB treatment register database
Number of treatment-experienced adults starting TB treatment	105	119	130	109	130	126	137	TB treatment register database
Number of notified TB cases, children	82	60	66	69	73	77	69	TB treatment register database
Percentage HIV-positive, all adults	5.2 [4-6]	- [4-6]	- [4-6]	- [4-6]	- [4-6]	- [4-6]	- [4-6]	Estimated from local antenatal care survey data

Table S17: Specified feasible ranges for calibration targets

Target	Feasible Range
Number of adults in the study setting	24,000 - 30,000
Number of children in the study setting	10,000 - 12,500
Percentage treatment-experienced, all adults	5.0 – 15.0
Percentage prevalent TB, treatment-naive adults	0 – 1.0
Percentage prevalent TB, treatment-experienced adults	0 – 6.0
Percentage HIV-positive, adults	2.6 - 10.4

S5.2. Initialization of the model

In the absence of published estimates for the prevalence of HIV, active TB and treatment-experienced individuals in the year 1992 (which marks the start of our simulation warm-up period), we determined the initial size of model compartments based on the following:

1. Prevalence of immunocompromised and non-immunocompromised HIV is sampled, respectively, from uniform distributions U [%3.5; %5.0] and U [%0.5; %1.0]. The prevalence of HIV-negative was set to 1 minus the sum of the above two samples.
2. Prevalence of the treatment-experienced within each HIV subgroup was sampled from the uniform distribution U [%6.0; %10.0]. The proportion of treatment-experienced with history of complete or incomplete TB treatment was set to be equal.
3. Within the HIV-negative subgroup:
    a. the prevalence of active TB was sampled from U [%0.4; %0.6] for treatment-naïve subgroup, and from U [%1.0; %10] for treatment-experienced subgroup;
    b. the prevalence of latent-TB among treatment-naïve was sampled from U [%40; %60].
4. Within non-immunocompromised HIV+ subgroup,
    a. the prevalence of active TB was sampled from U [%0.5; %2.0] for treatment-naïve subgroup and from U [%1.0; %10] for treatment-experienced subgroup;
    b. the prevalence of latent-TB among treatment-naïve was sampled from U [%55; %65]
5. Within immunocompromised HIV+ subgroup,
    a. the prevalence of active TB was sampled from U [%0.5; %2] for treatment-naïve subgroup and from U [%1.0; %10] for treatment-experienced subgroup;
    b. the prevalence of latent-TB among treatment-naïve was sampled from U [%55; %65]
6. Among children:
    a. Prevalence of active TB was sampled from U [%0.1; %1.0],
    b. Prevalence of latent-TB was sampled from U [%30; %70],
    c. Proportion recovered was sampled from U [%2.0; %10],
    d. Proportion susceptible was set to 1 minus the sum of the three samples above.

The initial size of compartments representing “on TB treatment” was assumed to be zero at the beginning of the simulation period.

S5.3. Calibration procedure

The goal of model calibration is to use the observations gathered throughout the epidemic to reduce the uncertainty around model input parameters. The calibration method employed here relies on the use of common random numbers [43, 44] to simulate epidemic trajectories. This variance reduction technique is often used to improve the accuracy of the comparison between two or more alternative configurations by using the same streams of uniform random variates in simulating these alternatives. This approach enables to retrieve any desired simulated trajectory when evaluating the performance of various control policies in the policy optimization step. In this method, to obtain one simulated epidemic trajectory, we first specified the seed of the simulation’s random number generator (RNG) object. The simulator then uses the RNG object to generate a unique stream of random numbers which will be used to both draw a sample for epidemic parameters and to generate one simulated trajectory. This approach enabled us to regenerate any desired trajectory by knowing the corresponding RNG seeds.

To describe our calibration approach, we defined the following notation:

- $\hat{Y} = [\hat{y}_{q,t}]$: matrix of observations where $\hat{y}_{q,t}$ denotes the observation on the qth calibration target during the year $t \in \{2002,2003,\ldots,2008\}$. Calibration targets are described in Tables S15,S16.
- N_q: number of observation points on calibration target q; for example, $N_q = 1$ for "Percentage treatment-experienced, all adults" and $N_q = 7$ for "Number of treatment-naïve adults starting TB treatment" (see Tables S15, S16).
- $Y_z = [y_{z,q,t}]$: matrix of simulated observation on the qth calibration target during the year $t \in \{2002,2003,\ldots,2008\}$ of a simulated trajectory for which RNG seed z was used.

For RNG seed z, we measured the similarity of the simulated time series $\{y_{z,q,t}: t = 2002,2003,\ldots,2008\}$ and observed time series $\{\hat{y}_{q,t}: t = 2002,2003,\ldots,2008\}$ as:

$$D(Y_z, \hat{Y}) = \sum_{q=1}^{Q} \sum_{t=2002}^{2008} w_{q,t}\left(y_{z,q,t} - \hat{y}_{q,t}\right)^2 / N_q, \quad (3)$$

where Q is the number of calibration targets and $w_{q,t}$ is the weight of observation $\hat{y}_{q,t}$. We chose $w_{q,t} = \frac{1}{e_{q,t}K_{q,t}}$, where $e_{q,t}$ is the error bound in observation $\hat{y}_{q,t}$, and $k_{q,t} = 1$ if the calibration target q was specified in percentage (e.g. active TB prevalence among treatment-naïve or treatment-experienced individuals) and $k_{q,t} = \left(\hat{y}_{q,t}\right)^2$, otherwise.

To build a set of trajectories to evaluate the performance of different control strategies, we first simulated $N_0 = 500{,}000$ epidemic trajectories, each of which uses parameter values that are randomly drawn from the *prior* probability distribution of epidemic parameters listed in Tables E1 - E14. Among these trajectories, we first eliminated those that violated pre-specified feasibility bounds shown in Table S17 (see also main manuscript, Figure 2). Let Z denote the set of RNG seeds that correspond to the remaining trajectories. To generate N epidemic trajectories for evaluating control strategies, for each simulation run, we selected a random sample of $z \in Z$ = 1,000 trajectories with the probability $\pi_z = \frac{p_z}{\sum_{z \in Z} p_z}$, where $p_z = e^{-D(Y_z,\hat{Y})}$. The probabilities π_z is proportional to the goodness of fit of each trajectory, hence a trajectory with better goodness-of-fit measure has a higher probability to be sampled. These final 1,000 trajectories were used for analysis (see below).

S6. Outcome definitions and data analysis

We projected trajectories of TB incidence, prevalence and mortality. Incident TB was defined in our model as the number of adults and children, regardless of treatment history and HIV status, who transitioned into any of the infectious TB compartments; individuals remaining infectious after incomplete treatment were not counted in incidence estimates. Prevalent TB was defined as the number of adults and children in any of the infectious compartments at a particular point in time. TB mortality was defined as the number of adults and children who died while either in any of the infectious or TB treatment compartments.

Best estimates of incidence, prevalence and mortality were derived by calculating the mean of values projected from the 1,000 sampled model trajectories. We calculated 95% percent uncertainty intervals representing the 2.5th and 97.5th percentiles of the 1,000 sampled trajectories. The impact of both interventions was defined as the cumulative number of incident and prevalent TB cases and TB deaths that was averted in the population (compared to the baseline scenario of no targeted interventions) during a 10-year period (2016 - 2025).

S7. Posterior estimates for the natural history of TB by history of TB treatment

Posterior estimates for parameters describing the natural history of TB among treatment-experienced and treatment-naïve people are shown in Figure S3-S6.

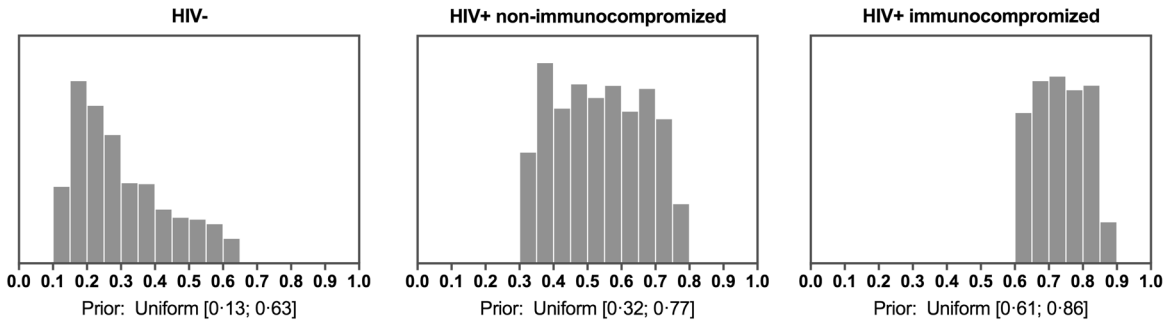

Figure S3: Posterior distribution for the relative risk of becoming reinfected among treatment-naïve, latently infected adults using the risk of primary infection among treatment-naïve, susceptible adults as a reference (assuming partial immunity afforded by prior infection)

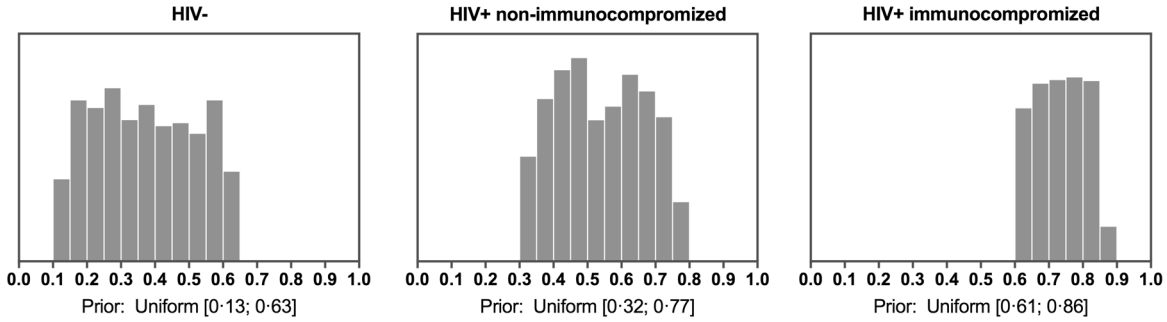

Figure S4: Posterior distribution for the relative risk of becoming reinfected among treatment-experienced adults using the risk of primary infection among treatment-naïve, susceptible adults as a reference (assuming partial immunity afforded by prior infection)

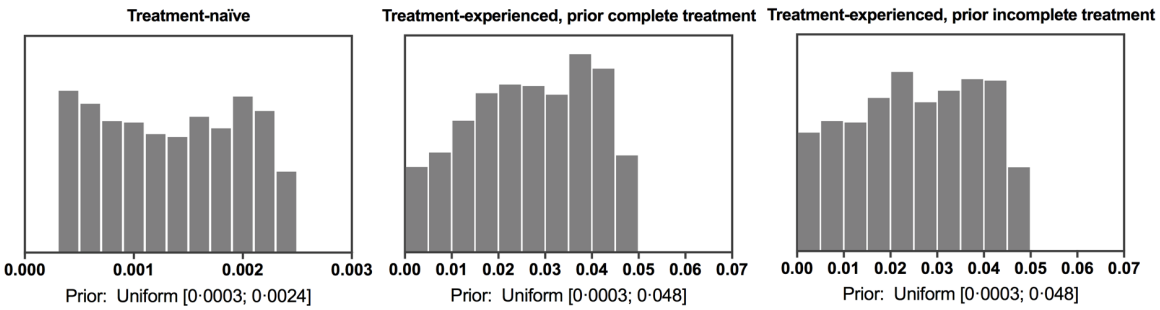

Figure S5: Posterior distribution for the reactivation rate among HIV-negative latently-infected adults, by history of previous TB treatment

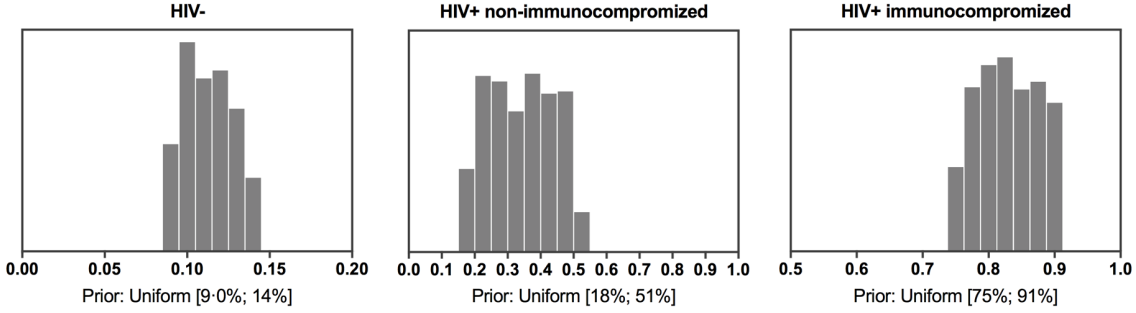

Figure S6: Posterior distribution for the probability of fast progression to active TB upon primary infection by status of HIV co-infection, treatment-naïve, susceptible adults

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